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Correlation of the non-invasive Cardiopulmonary Management (CPM) wearable device with measures of congestion in heart failure- CONGEST- HF

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Abstract

Background

The development of congestion is a leading cause of symptoms in people with heart failure (HF) and a major driver of prognostically important hospitalizations in these patients. Remote monitoring with implantable haemodynamic sensors has shown that subclinical elevations in intra-cardiopulmonary pressures occur days to weeks before a person may exhibit clinical indicators of congestion such as breathlessness or ankle oedema. Randomized controlled trials of implantable haemodynamic monitors have reported a benefit in reducing HF related events (hospitalizations or urgent outpatient visits) when treatment is guided by this monitoring. However, such sensors require a dedicated implant or an indication for an implantable device such as a defibrillator that can also provide diagnostic data for monitoring congestion markers. More recently, wearable devices have been developed that could also provide a remote monitoring option that is more generalizable to all patients with heart failure irrespective of ejection fraction and without the need for an invasive implant. The Cardiopulmonary Management (CPM) wearable device provides multi-parametric data on third heart sound energy (S3), thoracic impedance, tidal volume, heart rate and ECG.

Aims

The Correlation of the non-invasive Cardiopulmonary Management (CPM) wearable device with measures of congestion in heart failure (CONGEST-HF) study was a prospective, observational study designed to examine whether the CPM device measures correlated with

clinical measures of congestion in patients who were at risk of or actively receiving treatment for congestion.

Methods

I enrolled 3 cohorts into the CONGEST-HF study. Cohort A were patients undergoing a clinically indicated right heart catheterization as part of an advanced heart failure evaluation. Cohort A were assessed on one occasion on the day of the catheterization. Cohort B were patients with end-stage renal disease receiving haemodialysis. Cohort B had study assessments immediately before and after a scheduled dialysis session. Cohort C were patients admitted to hospital with decompensated heart failure who were being decongested with intravenous diuretics and were assessed for the study on day 1 on IV diuretics, day 2 on IV diuretics, the day of first dose of oral diuretics and on the day of discharge.

The primary analyses were the patient-individual Spearman correlations per cohort of: CPM device S3 and pulmonary capillary wedge pressure (PCWP) in cohort A; CPM device thoracic impedance and lung ultrasound (LUS) B-lines and change in thoracic impedance and change in B-lines and the volume of fluid removed by dialysis in cohort B; and CPM device thoracic impedance and device S3 and LUS B-lines and change in thoracic impedance and S3 and change in B-lines and change in weight in cohort C. Secondary analyses included Spearman correlations between CPM device tidal volume and tidal volume on bedside spirometry and between the CPM device measures and other right heart catheterization parameters (cohort A only) and (in all cohorts) echocardiography, blood biomarkers, physical signs and symptoms and ECG findings.

Results

66 patients in total were enrolled. In cohort A (20 patients), device S3 and PCWP measured at a single time point were not significantly correlated (r_{sp} = 0.296, p=0.204). In cohort B (21 patients), device thoracic impedance was strongly correlated with LUS B-lines both before (r_{sp} = -0.710, p<0.001) and after (r_{sp} = -0.769, p<0.001) dialysis but the correlation between change in both parameters was weaker and not statistically significant. Change in device thoracic impedance was correlated with volume of fluid removed by dialysis (r_{sp} = 0.495, p=0.024). In Cohort C (25 patients), change in both device thoracic impedance (r_{sp} = -0.638, p=0.002) and change in device S3 (r_{sp} = -0.530, p=0.014) were correlated with change in weight. CPM device S3 and LUS B-lines were correlated on the day of discharge (r_{sp} = 0.48, p = 0.029). There were no device related adverse events.

Conclusions

The CPM device demonstrated correlations with markers of intravascular and extravascular volume and change in these measures but not with haemodynamic pressures obtained at a single time point.

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Presentations during this period of research

- Correlation of the non-invasive Cardiopulmonary Management (CPM) wearable device with measures of congestion in heart failure- CONGEST- HF; Breaking Science session, ESC/HFA Congress, Lisbon 2024

- Prevalent and incident anaemia in PARADIGM-HF and effect of sacubitril/valsartan; ESC Congress 2022

- Effect of dapagliflozin on ventricular arrhythmias, resuscitated cardiac arrest and sudden death in DAPA-HF; Late-Breaking Science session - Heart Failure, ESC Congress 2021

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Author's Declarations

The work presented in this thesis was that of the author under the supervision of Professor Pardeep Jhund and Professor Roy Gardner. I performed all aspects of this study, including drafting the study protocol, the patient information leaflets and study documentation and the submissions for ethical and regulatory approval. All clinical study assessments were carried out by me except where I was unable to conduct study activity due to illness (performed in my absence by Dr Joanna Osmanska, Clinical Research Fellow, University of Glasgow), and the analysis of blood biomarkers (performed by Philip Stewart and Elaine Butler, University of Glasgow).

I declare that this thesis has been composed by myself and is a record of work performed by myself. It has not been previously submitted for a higher degree.

James P. Curtain

October 2024

1. CHAPTER ONE. INTRODUCTION

1.1 Definition of congestion

The proposed universal definition of heart failure (HF)[1], adopted by the European Society of Cardiology (ESC) in the 2021 ESC guidelines for acute and chronic HF[2], defines HF as a clinical syndrome with symptoms and/or signs caused by a structural and/or functional cardiac abnormality and corroborated by elevated natriuretic peptide levels and/or objective evidence of pulmonary or systemic congestion[1]. The emphasis on the presence of a constellation of features to support the diagnosis of HF is important clinically as once the diagnosis is made, each individual component of the definition may fluctuate according to the natural history of the condition or in response to treatment.

A hallmark of heart failure, as included in this definition, is the presence of congestion. There is no one formal definition of congestion, but broadly it is considered as a state of fluid accumulation in both the intravascular and interstitial spaces due to raised intra-cardiopulmonary pressures and deleterious neurohormonal actions in the kidneys leading to sodium and water retention. This is often, although not required to be, accompanied by a cardiac output that is inadequate to meet metabolic demands.

1.2 Epidemiology and Prognosis

The accumulation of congestion is the dominant feature of HF decompensation leading to hospitalization. HF hospitalizations are events of marked prognostic importance with in-hospital mortality in contemporarily managed patients in the UK estimated at 9%, increasing to 32% at one year post-discharge[3]. This 12-month all-cause mortality estimate has remained consistent in the UK over the past two decades, with a reduction in cardiovascular

mortality being offset by an increase in non-cardiovascular (CV) mortality, due particularly to infections and respiratory diseases[4]. In turn, infection or respiratory disease has been reported to be a major driver of HF decompensation, present in 15.3% - 28.2% of people with HF hospitalizations[5,6], underpinning the vulnerability and intertwined multi-morbidity that is present in these people. Internationally, the all-cause mortality incidence is similar to the UK with 38% of people enrolled in the USA-based ADHERE registry dying within 12 months of being admitted to hospital with decompensated heart failure[7]. Among 6,629 patients enrolled in the ESC-HF-Long Term Registry who presented with acute HF decompensation, 5,601 (84.5%) people had evidence of congestion either with or without end-organ hypoperfusion[8]. In the United Kingdom HF Audit 2023, among 63,644 validated admissions in England and Wales in 2021/22, approximately 79% of people had evidence of peripheral oedema on admission, and for 57% of the total cohort the oedema was graded as moderate-severe[3].

In clinical trials, the influence of a HF hospitalization on the occurrence of future HF hospitalizations is increasingly acknowledged, with contemporary trial outcomes designed to analyse recurrent events such as in the win-ratio[9-11]. In The Dapagliflozin and Prevention of Adverse Outcomes in Heart Failure (DAPA-HF) trial, among people who were receiving high rates of renin-angiotensin aldosterone system (RAAS) inhibitors, beta-blockers and mineralocorticoid receptor antagonists (MRA) at baseline, there were 809 HF hospitalizations in 548 patients over a median follow-up of 18.2 months (IQR 14.2 - 21.3). Demonstrating how patients who experience one hospitalization are at-risk for further events, 429 hospitalizations (53%) in DAPA-HF were recurrent[12]. The ability to monitor for

warning signs of emerging decompensation and act upon these signs has true potential as a therapeutic strategy.

1.3 Prognosis in the setting of clinically evident congestion

The implications of clinically evident congestion have been described in multiple reports. In multivariate analysis, the presence of moderate/severe peripheral oedema on admission was an independent predictor for both 30 day [Hazard Ratio (HR) 1.30 (95%CI, 1.12 – 1.51), p <0.001] and 1 year mortality [HR 1.13 (1.07 – 1.19)] in the 2023 UK HF Audit[3]. This has been extensively supported in clinical trials. In the landmark Prospective Comparison of ARNI with ACEI to Determine Impact on Global Mortality and Morbidity in Heart Failure (PARADIGM-HF) trial, the largest randomised controlled trial conducted in people with heart failure with a reduced ejection fraction (HFrEF), 2,526 of 8,380 (30.1%) ambulatory patients had at least one sign of congestion evident on examination at baseline[13]. Compared with people without clinical congestion, the adjusted-HR for the co-primary endpoint of HF hospitalization or CV death was 1.48 (1.34 – 1.65), 1.74 (1.49 – 2.03), 2.35 (1.90 – 2.90) and 5.96 (4.06 – 8.74) for people with 1, 2, 3 or 4 signs of congestion respectively. In order of prevalence, the most common signs were peripheral oedema (14.2%), an elevated jugular venous pressure (JVP) (9.7%), a third heart sound (S3) (9.5%), and pulmonary rales (7.9%). These frequencies and the incremental prognostic importance of escalating numbers of features of congestion are consistent with those reported in other trials[14-17].

1.4 Prognostic importance of changes in congestion

The association between congestion at a single time point and clinical outcomes also translates to change (either increasing or decreasing) in clinical congestion. The

disappearance of a sign of physical congestion between study visits in PARADIGM-HF was associated with an improvement in quality-of-life as indicated by a 5 point increase in the Kansas City Cardiomyopathy Questionnaire (KCCQ) – Overall Summary Score (OSS)[13], where a 5 point change is considered clinically meaningful and associated with a 10% decrease in the risk of death and hospitalization[18,19]. In the EVEREST trial, patients who were treated and had evidence of residual congestion on day 7 / discharge, compared with people whose signs of congestion had resolved, had a HR 1.07 (1.01 – 1.14) for HF hospitalization and HR 1.16 (1.09 – 1.24) for all-cause mortality per increasing feature of persisting congestion. On serial assessment of ambulatory patients with chronic HF, increasing severity of congestion by one physical sign was associated with an adjusted HR 2.00 (1.89 – 2.13) for HF hospitalization or CV death compared with no increase in congestion[13]. In the DOSE (Diuretics Optimization Strategies Evaluation) and Cardiorenal Rescue Study in Acute Decompensated Heart Failure (CARESS-HF) acute HF trials, rates of re-admission or death were markedly high among even patients who achieved a resolution in signs of congestion (50% at 60 days follow-up). The rate of this combined outcome was still lower in this group than compared with people who had persistent congestion (68% at 60 days, p = 0.038). However, in patients whose congestion had apparently resolved, 27% had relapsed to low-grade and 38% to high-grade evidence of congestion (orthopnoea and oedema) by 60 days highlighting the propensity for congestion to re-accumulate in vulnerable populations such as these trial cohorts.

1.5 Pathophysiology of congestion

While the clinical symptoms and signs commensurate with a patient having congestion are uniformly dyspnoea, orthopnoea, bendopnoea, bloating and oedema, S3, an elevated JVP

and pulmonary rales the development of such features do not follow one common pathway. Instead, congestion is the complex interplay between venous capacitance and intravascular homeostatic mechanisms that become disordered in decompensated HF. In this next section I will describe the different pathophysiological mechanisms that are responsible for §developing and sustaining congestion.

1.5.1 Intravascular congestion

Relative to the arterial system, veins are approximately 30 times more compliant[20] enabling them to act as capacitance vessels in which up to 70% of the body's blood volume is stored[21]. More than simply conduits returning blood from the micro-circulation to the heart, veins play a central role in the active regulation of cardiac filling and emptying, pre-load and cardiac output. The venous system balances between a large storage capacity or resting "unstressed blood volume" which is the volume of blood within a vein when the vasculature transmural pressure is equal to zero and a "stressed blood volume" which represents the volume of blood in a vein under a transmural pressure above zero. The "stressed blood volume" determines mean circulatory filling pressure and has a direct bearing on venous return. Approximately 30% of the venous system is held within the stressed volume and 70% as an unstressed volume. The splanchnic veins are more compliant than other veins and serve as the largest reservoir of "unstressed blood volume" accounting for the storage of up to 20% of total blood volume[21,22]. Changes in venous capacitance volume can be determined passively as a result of transmural pressure changes or actively due to fluctuations in the degree of venous smooth muscle contraction, allowing the unstressed volume to be mobilized or re-distributed to the central effective, stressed circulatory volume as required[23,24]. Bendopnoea, defined as dyspnoea on bending forward, provides a clinical

illustration of passive transmural pressure changes resulting in increased preload and elevated cardiac filling pressures when measured invasively[25].

Ambulatory patients with HF are advised to monitor their weight as a warning sign of fluid accumulation[2]. However, weight gain may not be apparent in as many as 40% of patients who present in acute decompensated HF[26,27]. Among 4,172 patients enrolled in the Acute Study of Clinical Effectiveness of Nesiritide and Decompensated Heart Failure (ASCEND-HF) trial, 1,396 (33.6%) either lost no weight or gained weight gain when hospitalized[28]. As a marker of fluid retention, the limited ability of weight gain or weight loss to predict the onset or relief of congestion, respectively, in many patients points to other mechanisms that drive increases in intracardiac pressures and the translocation of fluid into the interstitium or alveolar space. The concept that congestion may result from an alternative pathophysiology to fluid retention is supported by studies estimating blood volume at the time of decompensation using 131-labelled human serum albumin indicator-dilution techniques or in chronic HF patients with 99-technetium labelled red blood cells[29-32]. This work demonstrated that 34% of congested patients on admission were estimated to be normo- or hypovolaemic[30] and the proportion of normovolaemic patients increased up to 54% among people managed in the outpatient setting[29,32].

In the event of a precipitous threat to circulating blood volume (eg sepsis, haemorrhage) the splanchnic venous system can restore the depleted circulation, acting as a functionally sequestered supply of blood to be recruited in circumstances of hypovolaemia. The redistribution of blood from the splanchnic (abdominal) venous system to the central venous compartment (thereby increasing cardiac preload), is an important contributor to the expansion of intravascular volume and a vascular form of congestion without the net gain in

weight that is typically accounted for by endogenous fluid retention. This redistribution can happen abruptly, resulting in acute pulmonary oedema, or be in a consistent state with the consequence of persistent elevation in intracardiac pressures. In HF, a state of high neurohormonal activation accompanied by sympathetic nervous system mediated release of adrenaline and noradrenaline, the stimulation of α-adrenoreceptors within the splanchnic veins causes profound venoconstriction with resulting redistribution of blood volume to the central venous system[21,33]. The bearing the sympathetic nervous system has on this vasomotor action is evident from the large numbers of adrenoreceptors in the splanchnic venous system, with a fives times higher concentration in the mesenteric veins than arteries[34]. When sympathetic nervous system activity is reduced, the capacitance in the splanchnic reserve increases. In-vivo investigation of the effects of splanchnic nerve block in patients with decompensated HF resulted in temporary decreases in systemic vascular resistance, right atrial and pulmonary capillary wedge pressures (PCWP), indicating how dysregulation of this blood compartment propagates increased intracardiac pressures and the potential that modulation of the splanchnic nervous system may have in ameliorating the contribution the venous space makes to vascular congestion[35]. In contrast, a case series of human patients demonstrated a 200% increase in central venous pressure and 67% increase in stroke volume upon receiving direct splanchnic nerve stimulation for over 1 minute [36].

1.5.2 Tissue Congestion

Most patients who are hospitalized with a HF decompensation have features of both peripheral (tissue) fluid overload and compartmental fluid redistribution, although one mode of congestion may predominate and both may be contributory to each other.

Continuously increased hydrostatic pressures in the capillary vessels lead to tissue congestion. In a normal resting state, oncotic and hydrostatic pressures in vessels and the surrounding interstitium are in a steady equilibrium. During a HF decompensation, hydrostatic pressures rise within the venous system and oncotic pressure within the vessel decreases relative to the oncotic pressure in the interstitium, skewing the prior equilibrium towards the accumulation of fluid within the interstitium.

Glycosaminoglycans (GAGs) in the interstitium play an important role in the development of tissue congestion. Regardless of the tissue, the interstitium contains a gel-like substance made up of proteoglycans. The proteoglycans are in turn comprised of a central protein spine onto which multiple GAGs are attached. The GAGs from other proteoglycans connect by hydrogen bridges and give the interstitium structure. The GAGs are a binding site for water within the interstitium. Tissue congestion, evident clinically as pitting oedema, develops when the water molecules coalesce into larger vesicles and move freely within the interstitium and between cells[37]. While GAGs have a sodium-binding capacity that supports sodium homeostasis in HF[38-40], long-term saturation of the GAG network with sodium can denature the GAG form and weaken their ability to maintain the integrity of the interstitial structure and leave it vulnerable to the development of oedema if there is a minor elevation in venous pressure[23,38]. In addition to disruption of the GAG network, dysfunction of the lymphatic system also plays an important role in tissue congestion. The lymphatic system has the capability to increase its drainage 10 – 50 fold in the context of augmented pressures and maintains low interstitial colloid osmotic pressures by draining protein[41]. When lymph flow peaks, the rate of transudation from capillaries into the interstitium may exceed lymphatic capacity, leading to subsequent fluid accumulation in the interstitial space. As the

lymphatic ducts drain into the subclavian veins, an increase in central venous pressure may counter the lymphatic fluid draining from the vascular space and set a state beyond which lymphatic flow rates cannot increase[42].

The development of pulmonary oedema is subject to intravascular pulmonary capillary pressure becoming sufficiently elevated to overcome the perialveolar interstitial oncotic pressure. A pulmonary capillary pressure of approximately 28 mmHg (8 mmHg being normal) is considered to be a threshold for this to occur. In the setting of acute HF in well-compensated patients and those without a prior cardiac history, a rapid elevation to this threshold may be all that is needed to induce profound pulmonary oedema. In contrast, in patients who have chronically elevated pulmonary capillary pressures, adaptive changes in the lymphatic system can occur with dilatation and increase in flow of the lymphatics. In such patients, marked elevations in pulmonary capillary pressure can occur (up to 45mmHg) without the development of pulmonary oedema[43,44] .

1.5.3 Learnings from implantable haemodynamic studies

Analyses of the intra-cardiopulmonary pressure data obtained from early randomised trials of implantable haemodynamic monitors provided important insights into the natural history of HF decompensation, particularly the subclinical alterations that occur prior to the onset of symptoms or signs that lead a patient to present to their physician or nurse. In the Chronicle Offers Management to Patients with Advanced Signs and Symptoms of Heart Failure (COMPASS-HF) study, pulmonary pressures in patients with an EF<50% were found to rise an average of 29 ± 22 days before HF hospitalization occurred[45]. Intra-cardiopulmonary pressures rose steadily despite serial weight measures at 7 weeks, 4 weeks, 2 weeks and 1

day before the diagnosis of a HF-related event showing no statistical difference between measures[45]. This pattern is in keeping with the development of intravascular congestion as described above, whereby fluid is not necessarily retained but is redistributed to cause elevations in pressures. In CHAMPION, among people with an EF ≥40%, the increase in mean pulmonary artery (PA) pressure was greater before hospitalization for HF (3.4±4.6 mmHg) than hospitalization for any other reason (0.7±4.8 mmHg), *p*=0.017. The same pattern was observed in those with an EF ≤40% (1.3±5.6 Vs −0.3±5.5 mmHg, *p*=0.003)[46].

Not only have intra-cardiopulmonary pressures been observed to rise prior to hospitalization but the relationship between duration of time spent at maintaining an elevated pressure and the rise in pressures itself is important. In a retrospective analysis of data from the COMPASS-HF study, the product of pressure (P) x time (T) was calculated with baseline T being the point at which the lowest pressure was evident prior to change in pressure occurring in a unidirectional manner before a HF hospitalization. P x T was compared between patients who did or did not have a hospitalization (calculated from a randomly selected time period in those without a hospitalization). In patients with a hospitalization, the P x T was 221 ± 130 mmHg x days, with only 4% of the P x T values <60 mmHg x days. In comparison in patients who did not have a hospitalization, the P x T value was 5 ± 23 mmHg x days, with only 4% of the P x T values >60 mmHg x days ($p < 0.050$) [42]. In this study, neither the magnitude of the peak pressure, the change or rate in increase of the pressure were closely associated with the clinical deterioration when analysed separately. Instead, a small increase in pressure that occurred over an extended period was the haemodynamic factor most closely associated with the transition from a compensated to decompensated state

and may reflect the progressive escalation of pressure that overcame the protective factors such as lymphatic flow that would ordinarily buffer the development of congestion.

In a separate analysis of the COMPASS-HF trial, which excluded the seven days prior to a HF event, the relative risk of a HF event was lower in patients with a chronically lower average estimated pulmonary artery diastolic pressure <25 mmHg compared with a pressure ≥25 mmHg (adjusted hazard ratio = 0.32; 95% CI 0.19 to 0.53, p <0.001)[47]. There was an incremental increase in the risk of a HF event as chronic elevations in average pressure were observed: 20% with a chronic pressure of 18 mmHg, 34% with a chronic pressure of 25 mmHg, and 56% with a chronic pressure of 30 mmHg (p < 0.05)[47]. Among patients with a baseline median pulmonary artery pressure <25 mmHg who experienced an increase to >25 mmHg for the majority of their study days, the HF event rate was 1.10 / 6 study months compared with a rate of 0.23 / 6 study months in patients who remained on average at <25 mmHg (p <0.001). People who changed from a low baseline to a chronically high pressure had the same event rate as those whose baseline pressures were >25 mmHg and remained at >25 mm Hg. In comparison, among patients with the opposite haemodynamic trajectory with a high baseline day median pressure that decreased to <25 mm Hg for >50% of days, the HF event rate was 0.47/6 study months (p =0.042, compared with 1.10 for patients who remained at chronically high pressure). The lowest event rate was observed in patients whose baseline pressures were low and remained so through the study (0.23/6 study months). Such associations between elevations in pressures, particularly chronic elevations, and HF events gave weight to the hypotheses that monitoring and lowering pressure through treatment would reduce the potential for future hospitalizations.

1.6 Implantable haemodynamic trials

In this section I will summarise the important randomised controlled trials of haemodynamic monitors.

1.6.1 COMPASS-HF

COMPASS-HF was the first randomised study of an implantable haemodynamic monitor with the trials results published in 2008[48]. COMPASS-HF enrolled 274 NYHA III or IV patients across all ejection fraction (EF) ranges in a single blind study using the Chronicle (Medtronic Inc, Minneasota, USA) system. Chronicle was an implantable device similar to a single chamber pacemaker with an intra-cardiac pressure sensor near the tip of a lead sited in the right ventricular outflow tract or interventricular septum. The device continuously measured right ventricular (RV) pressures and change in pressures. Measures included estimated pulmonary artery diastolic pressure (ePAD), a surrogate marker of pulmonary capillary wedge pressure (PCWP) in the absence of pulmonary vascular disease. In prior feasibility studies, the Chronicle device had been shown to correlate strongly with invasively measured RV systolic pressure across implant (r = 0.96), 3 months (r = 0.95), 6 months (r = 0.94) and 12 months (r = 0.94)[49]. The device was implanted in all patients. Patients were randomised to management guided by or without knowledge of their pulmonary pressures. The study design attempted to select only a cohort with pulmonary hypertension (PH) driven by left heart disease. Patients with severe obstructive or restrictive pulmonary disease, primary PH or a congenital abnormality that would cause RV volume or pressure overload such as an atrial or ventricular septal defect and pulmonary valve stenosis were excluded. Similar exclusion criteria were adopted in subsequent implantable monitor trials[50-55]. As outlined above, elevations in ePAD occurred

between baseline and HF hospitalization (mean rise 4mmHg, p<0.001) and pulmonary pressures returned to baseline with treatment.

Over a study follow-up of 6 months, there was no difference between the interventional and control arm in the primary efficacy outcome of HF related events [hospitalizations and emergency or urgent care visits requiring intravenous (IV) therapy]. 84 events occurred in the Chronicle arm (event rate 0.67 / 6 months) versus 113 in 60 patients in the standard care arm (event rate 0.85 / 6 months), giving a statistically non-significant 21% reduction (p = 0.330) with haemodynamic guided treatment. In a retrospective analysis that was not pre-specified 37 Chronicle patients were hospitalized compared with 57 patients in the control group (HR 0.64, 95%CI 0.42 – 0.96, p = 0.030)[48]. 70 patients (25.5%) in COMPASS-HF had an ejection fraction ≥50% and 204 (74.5%) had an ejection fraction <50%. The relative risk reduction in HF hospitalization was comparable whether patients had left ventricular dysfunction or a preserved ejection fraction.

1.6.2 REDUCE-HF

In contrast to patients in COMPASS-HF who had advanced symptom burden (NYHA class III – IV) REDUCE-HF was a single-blind randomized controlled trial that enrolled patients with NYHA class II (milder) - III symptoms. These were patients who had an indication for an implantable cardioverter defibrillator, suggesting they were more likely to have a severely impaired left ventricle, and had had a recent hospitalization[52,53]. As in COMPASS-HF, the haemodynamic monitor being examined in the trial was the Chronicle device. The participant target enrolment number was 1,300 patients, but the study was stopped early due to concerns regarding lead failures in the Chronicle device from other prior studies. At

the point of study termination, only 400 patients had been recruited which substantially reduced the power to detect a difference between the intervention or control arm in the primary efficacy endpoint of HF-related events (defined as hospitalizations ≥24 hours or hospitalizations <24 hours requiring IV HF therapy, emergency department vis- its, or urgent clinic visits requiring IV therapy for HF). During a total of 4655 months of randomized follow-up (mean 11.6 months), there were 91 events in 43 patients from the intervention group and 90 events in 43 patients from the control group (p = 0.980). REDUCE-HF was the last trial to examine the efficacy of the Chronicle device.

1.6.3 CHAMPION

The CardioMEMS Heart Sensor Allows Monitoring of Pressure to Improve Outcomes in NYHA Class III Heart Failure Patients (CHAMPION)[50,56,57] studied a wireless pressure sensor (CardioMEMS, Abbott, Minneasota, USA), implanted into a distal branch of the pulmonary artery. The CardioMEMS system is a passive, wireless, radiofrequency sensor without batteries or leads. The sensor is a coil and a pressure-sensitive capacitor encased in a hermetically sealed silica capsule covered by silicone[57]. Two nitinol loops at the ends of the capsule serve as anchors in the pulmonary artery and allow sizing of the device to the pulmonary artery branch at implant. A right heart catheterisation (RHC) is performed at implant to calibrate the device. In prior experimental studies, CardioMEMS was strongly correlated with invasive RHC pulmonary artery systolic values [Spearman (r_{sp}) correlation coefficient, $r_{sp} = 0.96$, $p < 0.010$] and diastolic values ($r_{sp} = 0.88$, $p < 0.010$)[58]. The device provided pulmonary systolic, diastolic and mean pressure values uploaded daily by patients when lying on a proprietary pillow that transmitted data to the investigators for review.

Similar to COMPASS-HF and REDUCE-HF, CHAMPION was conducted in the United States only. The inclusion criteria were narrow being NYHA class III patients only, who had established HF with at least one previous admission. 550 patients were randomised to treatment with or without sensor guidance. Patients but not physicians were blinded to the group allocations in a single-blind trial design. The majority of patients (78%) had a reduced ejection fraction of <40%, 10% had milder left ventricular systolic impairment (EF 40-49%) and 12% had a preserved ejection fraction (EF≥50%).

The primary efficacy endpoint was a reduction in HF hospitalization over 6 months follow-up. 84 HF-related hospitalisations were reported in the treatment group (n=270) compared with 120 in the control group (n=280; HR 0.72, 95% CI 0.60–0.85, p=0.0002)[50]. Safety was also analysed with eight patients having device or system related complications (DSRC). Overall freedom from DSRC was 98.6% (97.3–99.4) compared with a prespecified performance criterion of 80% (p<0.0001). Overall freedom from pressure-sensor failures was 100% (99.3–100.0)[50]. These findings were maintained in a subsequent extended 18-month follow-up data analysis[51]. Given this was the first randomized trial to demonstrate a benefit in the use of implantable haemodynamic monitoring as a treatment strategy in patients with HF, an important mechanistic secondary endpoint “Change from baseline in pulmonary artery mean pressure at 6 months (mmHg×days; mean area under the curve)” demonstrated a significant reduction in pressures in the CardioMEMS guided arm compared with standard care (-156 mmHgxdays vs 33 mmHgxdays, p=0.008). Following the CHAMPION trial, implantable haemodynamic monitoring with the CardioMEMS device was given a class IIb recommendation in the 2016 and 2021 ESC HF guidelines[2,59].

1.6.4 LAPTOP-HF

The Left Atrial Pressure Monitoring to Optimize Heart Failure Therapy Study (LAPTOP-HF) was a prospective, multi-centre randomised controlled trial examining the efficacy of the HeartPOD left-atrial pressure sensor (St Jude Medical Inc, Minneapolis, USA)[60,61]. The HeartPOD sensor had previously been studied in the Hemodynamically Guided Home Self-Therapy in Severe Heart Failure Patients (HOMEOSTASIS) observational study with reductions in daily left atrial pressure demonstrated from 17.6 mmHg (95% CI 15.8 to 19.4 mmHg) in the first 3 months post-implant to 14.8 mmHg (95% CI 13.0 to 16.6 mmHg, p = 0.003) during the period of pressure-guided treatment[62]. As distinct from the other trials I described above, LAPTOP-HF was an unblinded study where physicians directed patients regarding the pressure sensor values in a self-management strategy. To be enrolled patients were required to have NYHA class III HF. There was no restriction on ejection fraction. The primary efficacy endpoint was the reduction in relative risk of HF hospitalization, including complications of HF treatment such as hypotension and acute renal failure. A data safety monitoring board stopped the trial at an early stage after 486 of a target 730 patients were enrolled due to safety concerns regarding the implant procedure. The study steering committee released interim 12-month data on those 486 patients. The annualized HF hospitalization rates in the experimental arm was 0.40 vs 0.68 in the control arm (relative risk reduction = 41%, p = 0.005)[60].

1.6.5 GUIDE-HF

Following the CHAMPION trial, there was continued interest in whether the CardioMEMS device could replicate a similar level of efficacy in a broader population of patients with HF. The haemodynamic-guided management of heart failure (GUIDE-HF) trial was designed to

test this hypothesis[54,55]. GUIDE-HF was the largest randomised trial to test an implantable haemodynamic monitor, enrolling 1,000 patients with NYHA class II – IV symptoms and either a recent hospitalization within the previous 12 months or an elevated natriuretic peptide level. The primary efficacy endpoint was a composite of all-cause mortality and total HF events (HF hospitalizations and urgent HF hospital visits) over 12-months of follow-up. There were 253 events in the treatment arm vs 289 events in the control arm giving a HR 0.88 (95% CI 0.74 – 1.05), p = 0.160[54]. When HF events alone were analysed the trend towards benefit in the CardioMEMS guided treatment arm was stronger (HR 0.85, 95%CI 0.70 – 1.03, p = 0.096). GUIDE-HF was an active trial when the COVID-19 pandemic emerged and potentially impacted the outcome of the study. A FDA-approved sensitivity analysis examining the primary endpoint up until the US national emergency declaration date (March 13th 2020) was performed because there was an observed reduction in control group events from the onset of the pandemic that may have attenuated benefit in the intervention arm. In this sensitivity analysis, CardioMEMS guided care appeared to reduce the relative hazard of the primary outcome compared with standard care alone by 19% (HR 0.81, 95%CI 0.66 – 1.00, p = 0.049).

1.6.6 Remote-monitoring in cardiac implantable electronic devices

Patients with HFrEF despite optimal medical therapy or survivors of a cardiac arrest are candidates for implantable cardioverter defibrillators, with or without cardiac resynchronization therapy[2,63]. The major device manufacturers have integrated device-based diagnostic algorithms, often multi-parametric, to detect indicators of HF decompensation. The important studies examining the efficacy of these algorithms is described below.

A key parameter in device diagnostics is the assessment of lung fluid which each of the devices estimates by analysing thoracic impedance between the right ventricular lead and the infraclavicular device generator. Early studies of the properties of lung tissue in both animal models and humans identified that when an electrical current was passed across the lung, the presence of intrathoracic fluid during pulmonary congestion allows for better conductance, causing a decrease in impedance[64-68]. Yu et al conducted an early, important proof-of-concept study following 33 patients with highly symptomatic HF (NYHA class III or IV) who had implantable cardioverter defibrillators and performed serial thoracic impedance measures over a two year period. 25 hospitalizations occurred in 10 patients, among whom thoracic impedance was observed to reduce by a mean 12.3% $\pm$ 5.3 ($p = 0.001$) over an average 18.3 days $\pm$ 10.1 prior to admission. Among the ten hospitalized patients, there was an inverse correlation between intra-thoracic impedance and both pulmonary capillary wedge pressure (PCWP) on invasive haemodynamics ($r = -0.61$, $p < 0.001$) and net fluid loss with decongestive treatment ($r = -0.70$, $p < 0.001$)[69]. This study provided plausibility to the hypothesis that thoracic impedance, measured within an existing implanted defibrillator, could be used as an effective method to monitor congestion in high-risk patients with HF and would form the basis for the subsequent studies described below.

1.6.6.1 PARTNERS HF

The PARTNERS HF (Program to Access and Review Trending Information and Evaluate Correlation to Symptoms in Patients With Heart Failure) was a prospective, multi-center observational study in patients receiving Medtronic (Medtronic Inc, Minneapolis, Minnesota, USA) cardiac resynchronization therapy (CRT) implantable cardioverter-defibrillators[70]. A combined HF device diagnostic algorithm (Cardiac Compass) was developed on an

independent dataset. The algorithm was considered positive if 2 of the following abnormal criteria occurred during a 1-month period: long atrial fibrillation duration, rapid ventricular rate during atrial fibrillation, high (> or =60) OptiVol fluid index measured by intrathoracic bioimpedance, low patient activity (<1 hour activity per day), abnormal autonomics (high night heart rate or low heart rate variability), or notable device therapy (low CRT pacing or implantable cardioverter-defibrillator shocks), or if they only had a very high (> or =100) fluid index. Patients in persistent or permanent atrial fibrillation at baseline were excluded. Compared with people who did not trigger a positive report, people who met the diagnostic criteria were five times more likely to progress to a HF hospitalization (HR 5.5, 95%CI 3.4-8.8, p <0.0001)[70]. The Cardiac Compass algorithm demonstrated reasonable negative predictive value with only 0.7% of people with a negative diagnostic result progressing to HF hospitalization in the subsequent 30 days. The algorithm is a feature in Medtronic implantable cardioverter defibrillators in current practice.

1.6.6.2 DOT-HF

The Diagnostic Outcome Trial in Heart Failure (DOT-HF) was an unblinded, randomised controlled trial that examined if monitoring intrathoracic impedance and other device-based diagnostic information could improve a combined outcome of HF hospitalization or all-cause mortality in HF patients who had an implantable cardioverter-defibrillator with or without cardiac resynchronization therapy[71]. This was a Medtronic sponsored study and was the first randomised trial to examine this outcome using an algorithm such as Cardiac Compass and OptiVol. Patients were randomised to an alert arm, including an audible patient alert for a reduced thoracic impedance, or to a control arm in which an alert were not available. If a device alert occurred, the protocol mandated a patient-physician contact. Of the collected

Cardiac Compass data, only changes in intrathoracic impedance with OptiVol could generate an audible alert. When the OptiVol index reached a pre-programmed threshold, patients in the access arm were alerted either by an audible sound from the device or by a hand-held patient indicator (patient check). Over a mean follow-up of 14.9 ± 5.4 months, 48 patients experienced a primary endpoint in the access arm and 33 people in the control arm (HR 1.52, 95% CI 0.97–2.37, p = 0.063). Substantially more people in the access (41 patients) versus control arm (24 patients) had an unplanned HF hospitalization (HR 1.79, 95% CI 1.08–2.95, p = 0.022). However, it was observed that symptoms and signs of HF (the typical triggers for an admission) did not differ between the groups. The increase in hospitalizations in the access arm was likely due to the alert and the physicians' interpretation that it required action. While other Cardiac Compass data were collected, the predominant measure to prompt an action from physicians was thoracic impedance, the only parameter that gave an alert. DOT-HF, provided insights into the limitations of remote monitoring namely, device-based alerts provided to people (either patients or physicians) may generate anxiety among parties leading to excessive intervention (such as unnecessary hospitalization) unless the response is appropriate to the clinical circumstance. Secondly, over-reliance on a single parameter that may provide false positives, can lead to actions that a multi-parametric algorithm would mitigate by providing a more complete, rounded assessment, particularly when the measures are surrogates or approximates of congestion such as impedance or patient activity.

1.6.6.3 OptiLink HF

The OptiLink HF (Optimization of Heart Failure Management using OptiVol Fluid Status Monitoring and CareLink) study was an unblinded multi-centre, randomised controlled trial

conducted in Germany[72,73]. The trial investigated whether early detection of pulmonary congestion by device measured thoracic impedance with a defined intervention algorithm would reduce all-cause death and cardiovascular hospitalizations in 1,002 patients with symptomatic chronic HF and a Medtronic implantable cardioverter defibrillator, compared to patients without telemedicine access. Over an average follow-up of 1.9 years, the primary outcome was not reduced in patients receiving telemedicine guided care compared to those without (HR 0.87, 95%CI 0.72 – 1.04, p = 0.130).

The OptiLink HF trial highlighted an important fallibility in the cycle of care required to effectively deliver clinical outcome benefit with remote monitoring. Only 30% of alerts for crossing the device-based fluid threshold were acted upon and 26% led to a medication change. There was no intervention in 38 of 110 cardiovascular hospitalizations which were preceded by crossing this fluid threshold, demonstrating that left to the discretion of physicians, medical intervention following device-based alerts may be low, particularly if patients are asymptomatic when reviewed following an alert or if there is variable confidence in device-based algorithms.

1.6.6.4 IN-TIME

The INfluence of home moniToring on mortality and morbidity in heart failure patients with IMpaired lEft ventricular function (IN-TIME) trial[74] was an international randomised controlled trial enrolling patients with severely impaired left ventricular systolic function, NYHA class II – III symptoms and a Biotronik (Berlin, Germany) implantable cardioverter defibrillator with or without cardiac resynchronization therapy. In keeping with other trials where atrial fibrillation occurrence was included in the detection algorithm, patients with

permanent or persistent atrial fibrillation at baseline were excluded. 664 patients were randomly assigned to either a telemonitoring group or standard, unmonitored care. Monitoring included the daily, or on detection, transmission of several pre-defined device collected events, including ventricular and atrial tachyarrhythmia episodes, implantable cardioverter defibrillator therapy, <80% biventricular pacing, increase in the frequency of ventricular extrasystoles, decreased patient activity, and abnormal intracardiac electrogram[75]. If a device detected event occurred, patients were contacted at the investigating clinician's discretion using standardised interview format to determine if the patient had features of worsening HF and if an in-person review or action was required. The control group had no such interaction. The primary outcome was a composite clinical score of all-cause death, hospitalization for HF, change in NYHA functional class or change in a patient-reported outcome measure. Over 12 months, 63 of 333 people (18.9%) in the telemonitoring group and 90 (27.2%) of 331 in the control group had a worsened composite clinical score (OR 0.63, 95% CI 0.43 – 0.90, p = 0.013), driven primarily by a large reduction in all-cause mortality (HR 0.36, 95% CI 0.17 – 0.74, p = 0.004) most of which were cardiovascular deaths (8 versus 21). There was however no difference in HF hospitalizations between the monitored and control group. Transmissions (which were automatic from the device) occurred on 85% of days per patient-year. 71% (238 patients) of the telemonitored group were contacted based on data transmissions, of whom 63 (26.4%) were scheduled for a clinical visit, amounting to 0.32 extra visits per patient-year. One potentially important observation was that patients with a history of atrial fibrillation appeared to benefit more from telemonitoring than patients without a history of atrial fibrillation (p value for interaction = 0.040) and device detection of atrial tachyarrhythmia was the event that most often led to patient contact, the early management of which may have reduced the potential

for worsening HF, stroke or mortality that can occur with atrial fibrillation in patients with HF[76-78]. Based on the findings of the IN-TIME study, the European Society of Cardiology guidelines for HF gave the use of multi-parametric algorithms in cardiac implantable electronic devices a modest class IIb recommendation for the remote monitoring of patients with symptomatic HF and an ejection fraction <35%[59].

1.6.6.5 MultiSENSE

The Evaluation of Multisensor Data in Heart Failure Patients With Implanted Devices (MultiSENSE) study was a prospective, observational study that examined the effectiveness of the HeartLogic algorithm (Boston Scientific, St. Paul, Minnesota, USA) to appropriately detect and predict worsening HF in patients who had received a cardiac-resynchronization therapy-defibrillator [79]. In keeping with the studies already described in this section, the MultiSENSE algorithm is multi-parametric, but was novel in that it was the first from a major manufacturer to quantify “heart sounds” by analysing intracardiac vibrations measured by a device accelerometer[80]. Other parameters included respiration rate, the ratio of respiratory rate to tidal volume, thoracic impedance, heart rate and activity level. The study compromised an algorithm development stage and subsequently a validation phase. An alert was issued when the threshold of the composite algorithm score (set nominally at 16) was crossed. The study co-primary endpoints were sensitivity to detect HF events and the unexplained alert rate. 900 people with symptomatic HF (NYHA class II to IV) and a cardiac-resynschronization therapy-defibrillator were enrolled, 500 into the development cohort and 400 into the validation arm across 81 international centres. In the development cohort, using the nominal threshold of 16, the observed sensitivity to detect HF events was 82%, and the unexplained alert rate was 1.33 per patient-year. In the validation group the

sensitivity was 70% and the unexplained alert rate was 1.47 per patient-year. The impact of the MultiSENSE study, as with most studies [apart from the IN-TIME trial[74]] examining the effectiveness of the device algorithms to improve outcomes for people with HF, is limited by the absence of supportive randomised trial data.

1.7 Wearable devices to detect congestion

Wearable technology is an emerging field in device-based tele-health. The clear advantage of wearables is their non-invasive applicability, and therefore generalisability to a broad population of patients with HF. In comparison, other forms of device based remote monitoring require a person to have an indication for an implanted device such as a defibrillator or necessitate an invasive dedicated implant as with the CardioMEMS system. However, limitations also exist. The wearable needs to be practical to apply and comfortable to wear if intended use is for a prolonged period. There is a continued tension between the amount of time a wearable should be worn by a patient and the duration required to capture meaningful data. Wearable devices, by design, cannot measure congestion directly such as a pulmonary artery sensor. To determine the practicality of using the wearable and its ability to detect congestion, validation of the device measures within a clinical cohort is crucial. I describe in this section the main wearable devices that have been developed for the assessment of congestion in patients with HF and the studies that examined their effectiveness.

1.7.1 Remote Dielectric Sensing System

Originally designed as a means for rescue teams to identify survivors amongst rubble, the Remote Dielectric Sensing System (ReDS) (Sensible Medical Innovations, Israel) is a wearable

vest that quantifies the percentage of lung fluid compared to lung volume by analysing the dielectric coefficient of the lung between the vest sensors. Different tissues have differing dielectric coefficients (water has a high coefficient, air has a low coefficient) with a normal ReDS value in the range of 20% to 35%[81-84]. ReDS technology had modest correlation with invasively measured PCWP in a cohort of patients with HF ($r = 0.49$, $p < 0.001$) and correlated more strongly with PCWP in transplant recipients ($r = 0.62$, $p = 0.001$)[82,83]. In a small cohort study of 50 patients recently hospitalized for HF, ReDS guided care reduced the rate of re-hospitalization (compared with the 90 days prior to the index event) by 93% (HR 0.07, 95%CI 0.01 – 0.54, $p = 0.010$). The findings were consistent when the rate of hospitalization for HF during the period of ReDS-guided care was compared with the 90 days following cessation of wearing the vest (HR 0.11, 95%CI 0.014 – 0.88, $p = 0.037$)[85]. Following these observation studies, the ReDS system was subsequently tested in the Sensible Medical Innovations Lung Fluid Status Monitor Allows Reducing Readmission Rate of Heart Failure Patients (SMILE) multi-centre randomised controlled trial which enrolled 268 patients with a recent HF hospitalization. Ejection fraction did not determine trial eligibility, although 71% of participants had HFrEF. Across an average follow-up of 6.1 ± 3.4 months, ReDS guided care, compared with the control arm, reduced HF readmission by 48% (HR 0.52, 95% CI 0.31-0.87, $P = 0.010$) in a per-protocol analysis. Whether an intention-to-treat analysis was performed is not clear from the available reports [86]. The ReDS system is approved by the Food and Drug Administration in the USA.

1.7.2 LINK-HF

The Multisensor Non-invasive Remote Monitoring for Prediction of Heart Failure Exacerbation (LINK-HF) study was a prospective, observational study designed to examine

the effectiveness of a personalized analytical platform using continuous data streams to predict rehospitalization after an admission for HF[87]. The Vital Patch (Vital Connect, San Jose, California, USA) was worn on the chest sternum for 24 hours a day for a minimum of 30 days and up to 90 days post-discharge. The sensor had 2 electrodes to analyse an ECG and bio-impedance measurement, a temperature sensor and a 3-axis accelerometer. Data collected were a continuous ECG, continuous 3-axis accelerometry, skin impedance, skin temperature, and information on activity and posture. Data derived from the primary information included heart rate, heart rate variability, arrhythmia burden, respiratory rate, gross activity, walking, sleep, body tilt, and body posture. The sensor transmitted stored data to an app on an Android phone which was encrypted and transferred by cellular connectivity at programmed intervals to a cloud analytics platform (PhysIQ, Chicago, Illinois, USA). Similarity-based modelling, analysing device collected parameters, was used to define a physiological baseline for the person within the first 72 hours post-discharge against which subsequent measures could be compared for change that may indicate improvement or deterioration in clinical status. In doing so, the LINK-HF study examined the predictive value of a personalized approach to data analytics. 100 patients were enrolled, the majority (74%) of whom had HFrEF. A key limitation was that 98 of these 100 participants were male, an indication that the device was not practical for women to wear continuously. 87 people completed the minimum, protocol defined period of monitoring (30 days) and data were collected for 74% of total study time. There were 24 worsening HF events. The sensor/analytics platform identified a clinical alert status prior to hospitalization for HF with a 76% to 88% sensitivity (depending on two pre-specified methods of analysis) and 85% specificity with a median time between alert and readmission of 6.5 (4.2–13.7) days. The Vital Patch is commercially available in the USA.

1.7.3 BMAD

The results of the Benefits of Microcor in Ambulatory Decompensated Heart Failure (BMAD) were presented at the American College of Cardiology conference 2023 but are yet to be published[88]. The μCor system (Zoll Medical Corporation, Chelmsford, Massachucetts, USA) is a wearable patch sensor that detects congestion using radiofrequency technology. Weekly data reports were transmitted to investigators and permitted medical intervention to be undertaken. While the study enrolled a control group in whom collected sensor data were not transmitted to investigators for action, this was a non-randomised study with the limitations of potential confounding between groups whose baseline characteristics are not available. 522 patients were enrolled within 10 days of a HF hospitalization, of whom 265 were in the monitored, intervention arm. The sensor was worn for 90 days. The primary endpoint was re-admission for a HF-related cause. There was a 37% relative reduction in the primary endpoint in patients receiving monitored care compared with the control arm, amounting to a 7% absolute risk reduction ($p = 0.030$). Despite the results of the study being unpublished, the μCor system has received Food and Drug Administration (FDA) regulatory approval in the USA and is commercially available.

1.8 Challenges of remote monitoring provision in the community setting

Several important challenges exist in the remote monitoring of patients with HF. These challenges may in part account for why no one device has established a role as a pillar of contemporary HF care in the way pharmacotherapies and defibrillators have.

Most remote monitoring devices require some degree of patient engagement. For instance, the CardioMEMS device obliges users to lie on a proprietary pillow to initiate a reading and transmit data and the investigational study device in this thesis required the use of a mobile

App to connect with the wearable device and activate a reading. With the mean age of a patient with HF being 78 years[3], the technical literacy and manual dexterity that is required to effectively use remote monitoring may pose a challenge to older, frail patients who have physical and cognitive deficits. Such pre-requisites may exclude certain groups of vulnerable patients who could benefit from closer monitoring but be unable to transmit data. While compliance with data transmissions in remote monitoring studies has broadly been high, most trials enrolled highly selected cohorts that are likely not representative of the wider population of people with HF. Demographically, these people are different to the average HF patient, where the mean age in the CHAMPION trial was 61 years, 17 years younger than the general HF population in the UK[3,50]. Additionally, people in trials have consented to participation and would be expected to be more committed to high rates of data transmission compliance than other people with HF. Device manufacturers also need to reconcile the tension between designing a device that records data for a sufficient period of time to capture clinically meaningful information against the burden of compliance. In the case of wearable devices, this is particularly relevant where devices such as the VitalPatch advise patients to wear the device on their chest for 24 hours a day. In the LINK-HF study, which examined the use of the VitalPatch, 98% of patients enrolled were male, indicating that wearing the device may have been impractical for women[87].

Remote monitoring is not simply a device but additionally requires a system of care. Large volumes of data need to be distilled into readily communicated clinical information that can be acted upon sensibly. The DOT-HF trial provides a salutatory example of how device data and action can have inadvertent consequences. In this trial, alerts that were audible to patients were triggered when a nominal thoracic impedance threshold was crossed. An unforeseen outcome of this model of care was a substantially increased number of

hospitalizations in the monitored arm of the study although there was no other evidence to confirm that those patients were at risk at the time of the alert[71].

1.9 The clinical assessment of congestion

During my PhD project I performed a multi-modal, detailed assessment of congestion on the study participants. In this following section I will describe the methods of assessing congestion that I employed in the study and discuss the literature that has informed the basis for using these methods, their strengths and limitations.

1.9.1 Right heart catheterization

The invasive measurement of intra-cardiopulmonary pressures by RHC is considered the gold standard for assessing congestion. Depending on the indication the ESC guidelines recommend performing RHC strongly (class I, for transplant or mechanical circulatory support evaluation) or more modestly (class IIb, for the diagnosis of HFpEF in selected patients)[2]. The test allows for the quantification of three parameters; pressure, flow (eg cardiac output) and vascular resistance[89]. Intravascular pressure is measured using a fluid-filled swan gantz catheter attached to a pressure transducer. A pressure wave is transmitted from the tip of the catheter to the transducer via the column of fluid in the catheter. The transducer is calibrated against a reference pressure and the setting of a zero reference is performed at the beginning of the procedure by levelling the transducer at the height of the atria (mid thoracic level). In broad terms, when fluid is added to a cardiac chamber or compressed within a chamber the pressure will usually rise. When the chamber relaxes or if fluid leaves the chamber, the pressure will reduce. In a standard RHC in patients with HF, the right atrial, right ventricular, pulmonary artery and pulmonary capillary wedge pressures are

measured, along with cardiac output (by the Fick or thermodilution methods) and pulmonary arterial oxygen saturations. In the Evaluation Study of Congestive Heart Failure and Pulmonary Artery Catheterization Effectiveness (ESCAPE) randomised trial, the use of pulmonary artery catheters to guide the in-hospital management of congestion demonstrated a reduction in haemodynamic parameters but did not provide a reduction in mortality over follow-up and incurred the consequence of more catheter-related adverse events [90,91]. The implication is that a single time-point or episodic haemodynamic monitoring may provide some short-term benefit, balanced against risk, but in a chronic disease such as heart failure the benefits of such interval or baseline data are mitigated by the progressive nature of the condition and the vulnerability these patients exhibit to decompensation over time.

1.9.1.1 Right atrial pressure

The right atrial wave form has three positive deflections. The *a* wave, due to atrial contraction, follows the *p* wave on the electrocardiogram. The height of the *a* wave is determined by the extent of atrial contractility and the resistance to right ventricular filling such as in pathological states like tricuspid stenosis or in instances of atrio-ventricular dissociation (complete heart block, ventricular tachycardia). The *x* descent follows the *a* wave and is due to right atrial relaxation and downward motion of the tricuspid annulus during right ventricular contraction. The *c* wave occurs during the *x* descent as the wave is reflected off the closing tricuspid valve. Pressure in the atrium subsequently rises as the atrium fills, representing the *v* wave, which corresponds in timing to right ventricular systole. The height of the *v* wave is related to the volume of blood returning to the right atrium (pre-

load) and the compliance of the atrium. When the tricuspid valve opens, the *y* descent occurs as blood passively exits the chamber into the right ventricle.

1.9.1.2 Right ventricular pressure

Ventricular diastolic pressure is typified by an early rapid filling wave during which most of the chamber fills, a slow filling phase and then an *a* wave marking atrial contraction of blood into the ventricle. The right and left ventricular systolic patterns are similar. However, the duration of systole, isovolumetric contraction and relaxation are longer and the ejection period shorter in left ventricular systole.

1.9.1.3 Pulmonary artery pressure

The outline of the pulmonary artery pressure waveform includes a steep systolic wave, the incisura or notch (resulting from closure of the pulmonary valve) and a steady decline in pressure until the subsequent systolic wave. In the absence of significant pulmonary vascular remodelling, the diastolic pulmonary pressure should equal the mean PCWP because the pulmonary circulation has low resistance. The diagnosis of pulmonary hypertension (PH) requires invasive catheterization[92], and is defined as mean pulmonary artery pressure (mPAP) >20 mmHg. The additional measures of PCWP and pulmonary vascular resistance (PVR) informs the categorization of PH into pre-capillary PH (mPAP >20 mmHg, PCWP ≤15mmHg, PVR >2 Wood units), post-capillary PH (mPAP >20 mmHg, PCWP >15mmHg, PVR ≤2 Wood units) or combined pre/post-capillary PH (mPAP >20mmHg, PCWP >15mmHg, PVR >2 Wood units).

1.9.1.4 Pulmonary capillary wedge pressure

The PCWP reflects left atrial pressure and has a similar waveform which resembles the right atrial pressure tracing apart from the *v* wave tending to be higher than the *a* wave on the left side. In the absence of significant mitral valve disease (eg mitral stenosis) the left atrial pressure, represented by the PCWP, should approximate to left ventricular end-diastolic pressure.

1.9.1.5 Systemic vascular resistance

Vascular resistance calculations are based on the hydraulic principles of fluid flow, where resistance is the ratio of the drop in pressure between two points in a vascular circuit and blood flow through it[93]. Systemic vascular resistance (SVR) is the resistance against which the left ventricle must work to eject its stroke volume. SVR is calculated in dynes from the following equation:

$$\frac{\text{Mean arterial pressure} - \text{right atrial pressure}}{\text{Cardiac Output}} \times 80$$

SVR is usually elevated in decompensated HF, particularly in low cardiac output states. Conversely, it is often low in high-output cardiac failure secondary to hyperthyroidism or liver disease or in vasodilatory sepsis.

1.9.1.6 Pulmonary vascular resistance

Pulmonary vascular resistance (PVR) is the resistance against blood flow from the four pulmonary veins to the left atrium. The transpulmonary gradient is calculated as the mean pulmonary artery pressure – PCWP. PVR is then calculated from the following equation:

$$\frac{\text{Transpulmonary gradient}}{\text{Cardiac Output}}$$

Clinically, PVR is an important determinant of transplant eligibility, where an irreversibly elevated PVR (>3 Wood units) is a contra-indication to transplant due to concerns that the donor right ventricle will fail if grafted into a pulmonary circulation with fixed elevated resistance. In HF, PVR usually increases because of World Health Organization group 2 PH from elevated left-sided pressures and may be ameliorated with diuretics and afterload reduction.

1.9.1.7 Cardiac Output

Most commonly, cardiac output can be calculated by two methods, the Fick equation and thermodilution. The Fick principle estimates cardiac output assuming that pulmonary blood flow is equal to systemic blood flow in the absence of an intracardiac shunt, with the flow of blood being proportional to the difference in oxygen concentration between arterial and venous blood and the rate of uptake of oxygen by blood in the lungs. The equation for determining cardiac output from the Fick priniciple is:

$$\frac{\text{Oxygen consumption (mL/min)}}{}$$

Arterial-venous oxygen saturation difference x 1.36 x Haemoglobin x 10

Compared to the thermodilution method, the Fick method is more accurate in the setting of low cardiac output and significant tricuspid regurgitation. It is limited by a requirement to avoid supplemental oxygen at the time of the blood sampling and should be interpreted with caution in patients with significant mitral or aortic regurgitation[94].

The thermodilution method is an alternative to the Fick calculation. Cold saline is injected into the catheter which is sited in the main pulmonary artery. The change in temperature between the proximal and distal port of the catheter is measured by a thermistor in the distal catheter. The change in temperature versus time is graphed, with cardiac output being inversely proportional to the area under the thermodilution graph curve[95]. A greater area under the curve relates to a lower cardiac output. Advantages of thermodilution include quick, digitised results, the lack of need to withdraw blood and it is less affected by recirculation compared with the Fick approach. However, in patients with low cardiac output thermodilution may over-estimate cardiac output and it is inaccurate in significant tricuspid or pulmonary regurgitation[93].

Table 1-1 Normal values for measures obtained during right heart catheterisation[93]

Pressure (mmHg)	Average	Range
Right atrium (mean)	3	1 – 5
Right ventricle		
Systolic	25	15 – 30
Diastolic	4	1 – 7
Pulmonary artery		

Systolic	25	15 – 30
Diastolic	8	4 – 12
Mean	15	9 – 19
Pulmonary capillary wedge (mean)	8	4 – 12
Vascular resistance		
Pulmonary (Wood Units)	0.8	0.2 – 1.6
Systemic (Dynes)	1100	700 - 1600

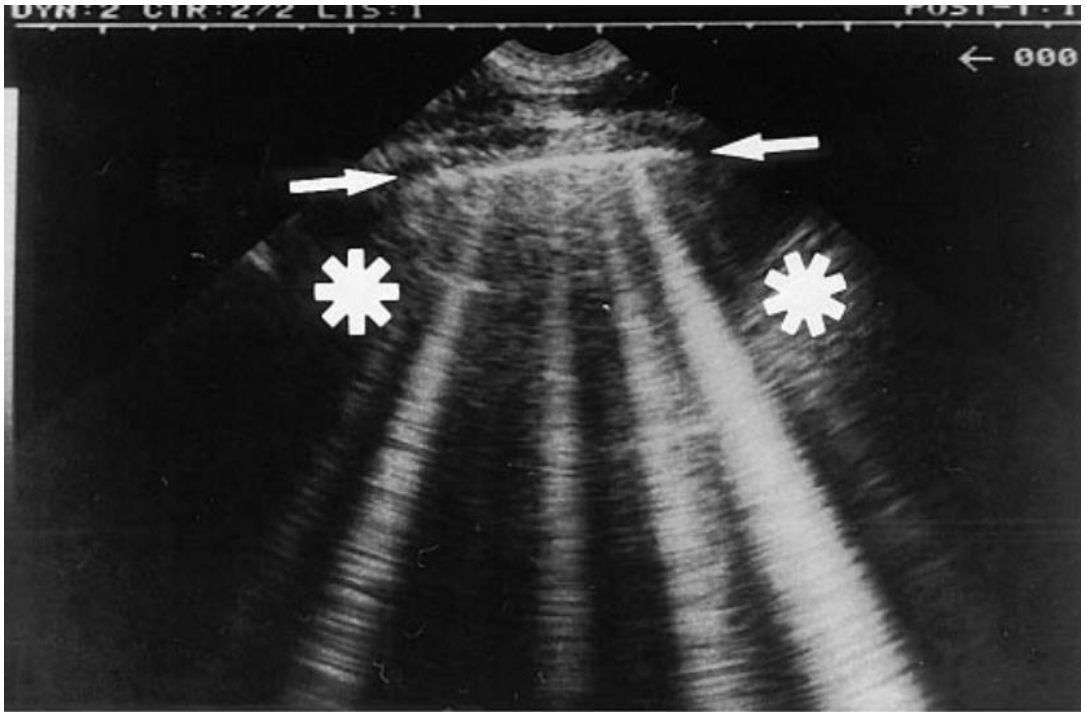
RHC has been used as the gold standard reference test against which invasively implanted devices such as the Chronicle and CardioMEMs devices were calibrated, with very high correlations between device and RHC measures (correlation coefficients, r = 0.96[49,58]). As these devices also sensed pressure invasively it was intuitive that RHC would be used as the reference measure. In doing so, confidence was obtained that the device produced haemodynamic estimations of reliable accuracy. Other measures of congestion, such as lung ultrasound (LUS) and NT-proBNP, are often used to determine the presence or absence of congestion and are assessed frequently in the management of patients with HF because of they are minimally invasive and readily repeated, unlike RHC. However, both of these measures have at best, modest correlation with invasive haemodynamics. When used as a reference measure against which to correlate other measures of congestion, parameters other than RHC are limited by being a “standard of care” in routine clinical practice but not the “gold standard” in terms of accuracy, an important limitation in the correlation between two surrogate estimates of congestion.

1.9.2 Lung ultrasound

LUS has steadily emerged over the past twenty years in clinical practice as a readily performed tool for assessing lung congestion in patients with acute HF[2,96-100]. Narrow, repetition artifacts are observed from the pleural line and extend to the far-field of the ultrasound screen when imaged using either a phased array or linear transducer[101,102]. These lines are observed in patients with interstitial syndrome such as pulmonary congestion and are termed “comet-tails” or “B-lines”. B-lines may also be detected in other conditions, including interstitial fibrosis, acute respiratory distress syndrome and some infections including COVID-19[102,103]. The use of LUS in addition to clinical assessment was found in an international, randomised controlled trial to have higher accuracy in the diagnosis of acute HF in the emergency department than clinical assessment alone, or the combination of chest X-ray and natriuretic peptide[104]. LUS has also been shown to be sensitive to change with reductions in B-lines observed both in acute HF following decongestive treatment [102] and in patients with end-stage renal failure who are having fluid removed intermittently by dialysis[105,106]. LUS B-lines have demonstrated modest correlation with PCWP ($r = 0.48$, $p = 0.010$) and correlated more robustly with extravascular lung water as quantified by the PiCCO system (Pulsion Medical Systems, Feldkirchen, Germany) ($r = 0.60$, $p < 0.001$)[107] in patients who have undergone cardiac surgery or in ventilated patients in the intensive care unit ($r_{sp} = 0.91$, $p < 0.001$)[108]. In patients undergoing coronary angiography, LUS B-lines have demonstrated correlation with left ventricular end-diastolic pressure (LVEDP) ($r_{sp} = 0.62$, $p <0.001$), a relation that was evidently stronger than concomitantly captured echocardiographic parameters[109]. LUS has correlated strongly with other non-invasive measures of congestion, including N-terminal pro B-type natriuretic peptide (NT-proBNP) ($r = 0.69$, $p < 0.001$) in patients with acute dyspnoea in the emergency department[110]. The

value of LUS extends to improved clinical outcomes, with reductions in hospitalization for HF being observed in randomised trials of patients who had LUS-guided care in the acute setting and in outpatients[111,112]. These benefits may be explained by an increase in diuretic titration (up or down) in patients who receive LUS guided care[113].

Figure 1-1 Comet tails (sonographic B-lines) on lung ultrasound in a patient with pulmonary congestion[97]



1.9.3 Echocardiography

The primary purposes for echocardiography in HF are for assessment of chamber size, cardiac systolic and diastolic performance and valve function and the identification of any precipitating causes such as regional wall motion abnormalities in ischaemia or biventricular hypertrophy consistent with amyloidosis [114,115]. Several echocardiographic parameters are used to estimate filling pressures and volume status. In this section I will describe the

parameters I measured during the PhD and their utility in the assessment of congestion in patients with volume overload.

1.9.3.1 E/e' Ratio

The E/e' measure is calculated from the ratio of early filling velocity on transmitral Doppler (E) / early relaxation velocity on tissue Doppler (e'). The average of the measured lateral and septal E/e' values are used in the calculation. An E/e' >9 at rest is considered as a threshold for diastolic dysfunction or elevated left ventricular filling pressure[2]. A higher average E/e' threshold of >14 is proposed by the American and European Associations of Cardiovascular Imaging on the basis that specificity is increased and false positives are reduced[114], with recognition that intermediate values between 9 – 14 often produce variable correlation with PCWP and other non-invasive echocardiographic estimates are required[116,117]. As with other echocardiographic estimates of filling pressures it is limited by the quality of imaging including the ability to sample the appropriate segment of the mitral annulus.

The performance of E/e' has varied depending on the population studied. In one study of 100 patients with HF, across the range of EF, E/e' < 8 accurately predicted normal mean LVEDP (<12 mmHg) and E/e' >15 predicted raised LVEDP (>12mmHg). Between 8 – 14, there was wide variation in LVEDP measurements. E/e' appeared to correlate better with mean LVEDP in patients with systolic dysfunction (EF<50%) (r = 0.60) and less so in patients with preserved systolic function (EF >50%) (r = 0.47)[117]. In a broad population of 118 people with undifferentiated breathlessness, E/e' was shown to have weak correlation with PCWP (r = 0.36, p <0.001)[118]. Another study of 106 patients with advanced systolic heart failure also reported poor correlation between E/e' and PCWP (r = 0.18, p = 0.070). 51 (49%) of these 106 patients underwent a follow-up assessment, and change in E/E' and change in PCWP

when analysed in this subgroup were again poorly correlated (r = 0.23, p = 0.100)[119]. In patients with HFpEF, a meta-analysis of nine studies examined the correlation between five echocardiographic parameters used in the diagnosis of HFpEF and invasively measured haemodynamics (PCWP in five studies and LVEDP in four studies) [120]. The strength of the correlation between E/e' and invasive haemodynamics was broad, ranging from r = 0.19 (p = 0.390)[121] to r = 0.84 (p <0.001)[122], with a pooled random effects estimate that reported modest correlation (r = 0.56, p <0.05)[120]. Per unit increase in E/e', in the pooled estimate, there was a 5% increase in the risk of mortality or hospitalization for HF (HR 1.05, 95%CI 1.03 – 1.06).

1.9.3.2 E/A ratio

The E and A waves are measured when a pulsed-wave sample volume is placed at the tip of the mitral leaflets. The measured peak velocity reflects the relative instantaneous change in pressure between the left atrium and ventricle after the opening of the mitral valve. The acceleration of blood flow velocity is seen on transmitral flow as the E wave which represents passive filling into the left ventricle. A deceleration of flow subsequently occurs, the rate of which depends on the effective compliance of the ventricle. Flow across the valve further accelerates again when the atrium contracts represented by the A wave. An E/A ratio ≥2 indicates LA mean pressure is raised and restrictive filling is present (grade 3 diastolic dysfunction). A ratio ≤0.8 is in keeping with mildly impaired (grade 1 diastolic dysfunction). A ratio between >0.8 – 2 can represent either normal function or be a pseudonormal, moderately impairment state (grade 2 diastolic dysfunction) and further parameters including E/e' >9, TR vmax >2.8m/s and LA volume index >34ml/m^2 are measured to differentiate between these two grades[2,114]. E/A ratio cannot be performed in patients with

atrial fibrillation as no A wave is present, and is age dependent being reduced in older people. As a measure of flow and also LA pressure, E/A ratio has shown correlation with PCWP. Among 107 patients with a recent myocardial infarction and severely impaired left ventricles, the correlation coefficient between E/A ratio and PCWP was r = 0.69, p <0.001. In this study, patients with an E/A ratio >1 compared with people with an E/A ratio <1 were 4 times more likely to die[123]. Similarly, in 140 patients with chronic HFrEF, the E/A ratio correlated significantly with PCWP (r = 0.65, p <0.001), however the strength of this relationship was modified by the E/A value. If E/A was ≥2 (restrictive filling) the correlation coefficient was r = 0.55, p <0.001, with 23 of 24 patients in this group having a PCWP ≥20 mmHg. Conversely, if the E/A ratio was in the intermediate range of ≥1 to <2 then the correlation with PCWP was negligible (r = 0.08), and 23 of 58 (39.6%) of this group had a PCWP ≥20 mmHg, indicating that an elevated E/A ratio has high specificity for predicting an elevated PCWP but low sensitivity[124].

1.9.3.3 Pulmonary Valve Acceleration Time (PVAT)

Measured in the parasternal short axis view, the PVAT is analysed by pulse wave Doppler in the right ventricular outflow tract at the level of the valve in systole, from the onset of flow to the peak velocity. A PVAT <105ms indicates pulmonary hypertension[92,125]. The presence of a mid-systolic notch on the Doppler envelope is also indicative of pulmonary hypertension and has been associated with an elevated PVR compared with people without a notch and an 18% increase in mortality per 20 ms decrease in PVAT value[125,126].

1.9.3.4 Inferior Vena Cava (IVC)

Visualized in the subcostal view, the IVC and the extent of its collapsibility of respiration provides an estimate of right atrial pressure if pressures are high or low but is less reliable for intermediate atrial pressure values[127,128]. IVC estimation of right atrial pressure may be inaccurate in people who are pregnant, have undergone liver transplantation, ventilated patients. As right atrial pressure increases this transmits back into the IVC, causing the IVC to dilate and reducing its reactivity to inspiration during which it usually collapses if pressures are within normal range. The smaller the vessel diameter and greater the degree of collapse, the stronger the indication of hypovolaemia. The IVC is expected under conditions of normal RAP (<5mmHg) to measure less than 21mm and to collapse >50%[127]. Measurements of the diameter of the IVC in M-mode and by 2-D assessment have shown high correlation with each other ($r = 0.88$)[129]. Measured in the supine position, IVC diameter correlated modestly with right atrial pressure in 53 patients with HF of mixed aetiology undergoing RHC ($r = 0.57$, $p<0.001$)[130]. In another study of 918 patients with congenital heart disease, IVC maximum diameter and invasively measured right atrial pressure were similarly correlated ($r = 0.56$, $p <0.001$)[131]. Using planimetry to assess IVC area the correlation between atrial pressure and IVC area has been reported to be stronger ($r = 0.71$, $p<0.001$) but this is more technically difficult to achieve visualization adequate enough for reproducible measures[130]. Prognostically, a dilated IVC is associated with 2 – 3 fold increase in the relative hazard of hospitalization for HF or death in patients with ambulatory, chronic HF irrespective of doppler-estimated pulmonary pressures [132-134].

1.9.3.5 Tricuspid Regurgitation Maximum Velocity (TR vmax)

Right ventricular systolic pressure (RVSP) can be determined from the maximum TR jet velocity, using the simplified Bernoulli equation (RVSP = $4V^2$ where V = TR jet velocity). This value is combined with an estimate of the right atrial pressure based on the IVC diameter and its collapsibility. Normal peak TR gradient resting values are $\leq$2.8 m/s with a low probability of pulmonary hypertension. Values between 2.9 to 3.4 m/s indicate a medium probability of pulmonary hypertension and a value >3.4 m/s confers a high probability[135]. In a study of 127 patients undergoing RHC and simultaneous echocardiographic assessment, TR vmax and the maximum systolic gradient between right atrium and ventricle were strongly correlated (r = 0.96, p <0.050)[136], a relationship that was repeated in further analyses[137,138]. Elevated TR vmax has been associated with a 1.5 to 2 fold increase in mortality in observational studies of general populations of patients undergoing echocardiography[139,140].

A notable limitation of the method is the underestimation of RVSP in patients with very severe TR. This occurs because the Doppler envelope may be cut off due to early equalization of right ventricular and atrial pressures, and the simplified Bernoulli equation then underestimates the RV-RA gradient. Additionally, patients with progressive right ventricular failure may be unable to generate a pressure gradient and a falling RVSP in the setting of worsening right ventricular function is a marker of poor prognosis. Notwithstanding these limitations, the ESC guidelines recommend the use of TR vmax as the preferred parameter in the assessment of pulmonary hypertension without the inclusion of IVC assessment due to potential errors in measuring the latter [92].

1.9.3.6 Left Ventricular Global Longitudinal Strain (LV GLS)

Strain is the change in length of a myocardial segment divided by the original length and expressed as a percentage and represents the magnitude of myocardial deformation during systole. The maximum longitudinal displacement of the myocardium can be measured by speckle-tracking echocardiography with a positive (plus %) denoting positive strain (lengthening) and negative strain (minus %) representing contraction. LV GLS is acquired from the apical 2, 3, 4 chamber views, with a normal range value being -20% or more negative[141-143]. Among patients with non-ischaemic dilated cardiomyopathy, LV GLS has been reported to correlate, albeit weakly, with PCWP ($r = 0.38$, $p = 0.010$)[144], while LV GLS has been observed to perform moderately well at discriminating between patients with or without PCWP $\geq$15 mmHg (AUC 0.75, 95%CI 0.61 – 0.89)[145]. Current international guidelines recommend the use of strain imaging by 2D echocardiography [141,143] but increasing interest in the use of 3D longitudinal strain has developed. In one small cohort study, GLS on 3D echocardiography demonstrated modest correlation with invasively measured LV end diastolic pressure ($r = 0.60$, $p < 0.010$)[146]. Abnormal GLS is strongly associated with increased mortality in patients with HF[147,148], and high proportions of patients admitted with HF to hospital have been demonstrated to have impaired LV GLS [149]. Conversely, improvements in LV GLS have been associated with a reduced risk of death in patients with HF[150]. However, few studies have examined the relationship between change in strain and markers of decongestion.

1.9.3.7 Left atrial volume (LAV)

In the absence of atrial fibrillation or significant mitral valve disease, LAV indexed to body surface area (>34 ml/m^2) (LAVI) indicates chronically elevated left ventricular filling

pressures. In an early study of 40 patients referred for RHC, LAV showed correlation with PCWP ($r = 0.62$, $p < 0.050$)[151]. The strength of this relationship varied in subsequent studies and populations examined. Among patients enrolled in the Japanese Prospective, mUlticenteR, obServational stUdy of patIenTs with Heart Failure with Preserved Ejection Fraction (Pursuit HFpEF) registry who were in sinus rhythm with HFpEF, in whom LAV dilatation is a diagnostic criterion, the relationship with PCWP was reported to be weaker ($r = 0.34$, $p = 0.025$)[152]. In the EACVI Euro-Filling study, LAV was weakly correlated with LV end diastolic pressure in all included patients who were undergoing elective cardiac catheterization ($r = 0.28$, $p = 0.0003$). In this study there was a distinction between patients with or without systolic impairment (LVEF <50% or ≥50%), where in people with systolic dysfunction LV end diastolic pressure and LAV were correlated ($r = 0.36$, $p = 0.020$) but this relationship was not present in people with an LVEF ≥50% ($r = 0.10$, $p = 0.260$)[153]. Analyses of patients in atrial fibrillation have shown consistency with the strength of the relationships reported between people in sinus rhythm and PCWP. In atrial fibrillation, where the LAVI threshold is higher at >40 ml/m^2, LAVI demonstrated modest correlation with PCWP ($r = 0.42$, $p<0.050$)[154]. When measured by 3D echocardiography, maximum left atrial volume has also demonstrated modest correlation with PCWP ($r = 0.46$, $p < 0.001$)[155]. When considering the varied correlation between invasive haemodynamics and LAV, there is a fundamental limitation of examining a relationship between both parameters when filling pressures are measured at a single time point but LAV reflects a progressive, chronic process.

1.9.3.8 Left ventricular outflow velocity time integral (LVOT VTI)

Left ventricular outflow velocity time integral (LVOT VTI) provides an estimate of stroke distance or the distance in centimetres travelled by blood being ejected from the left

ventricle when the pulse wave doppler sample is taken from the LVOT at the level of the aortic valve. Across a defined cross sectional area (eg the LVOT) it can be used to calculate a doppler estimate of stroke volume and cardiac output. The normal range is 18 – 22cm. Reduced LVOT VTI has demonstrated a prognostically significant association with mortality (HR 2.06, 95%CI 1.21 – 3.49, p = 0.008 for LVOT VTI <19cm) in multivariable analyses[156], independent of ejection fraction[157,158]. LVOT VTI has only been correlated with invasively measured stroke volume in small studies with variable results, ranging from poor correlation in patients undergoing cardiac surgery (r = 0.26, p = 0.262) to weakly correlated in patients with HFpEF (r = 0.35, p =0.048)[159,160]. No studies have reported on serial measurements of LVOT VTI while patients have been decongested.

1.9.3.9 Mitral valve inflow deceleration

Measured by pulse wave doppler the duration of mitral valve inflow deceleration is measured from the peak E wave along the slope to the baseline. The normal range is 150 – 200 ms. A reduced deceleration time reflects rapid equalization of pressures between the left atrium and ventricle and is a measure of the effective operative chamber compliance of the left ventricle and an indicator of restrictive physiology [161-163]. When assessed within 3 weeks after a myocardial infarction in 107 patients with an EF <40%, deceleration time correlated modestly with PCWP (r = -0.55, p = 0.001)[123]. Among 140 patients with established ischaemic cardiomyopathy and severely impaired left ventricles, mitral valve deceleration time was reported to have very strong correlation of PCWP (r = -0.90, p <0.001)[124]. The strength of this correlation does not appear to be diminished by the presence of atrial fibrillation[164]. However, in other conditions such as in hypertrophic cardiomyopathy, deceleration time did not show any significant correlation with PCWP, while

in the same study the relation with PCWP in a separate cohort of patients with HFrEF was consistent with other aforementioned studies ($r = -0.73$, $p < 0.001$)[165]. With apparent discrepancies between groups, the implication is that left ventricular filling is subject to multiple interrelated factors that likely differ between populations and mitral valve inflow assessments have more or less utility depending on the cohort being examined. Serial measurements of deceleration time in patients undergoing decongestion have not been described.

1.9.3.10 Left ventricular ejection fraction (LVEF)

Left ventricular ejection fraction (LVEF), the most widely quoted measure of LV systolic function, is derived from the following formula: (LV end diastolic volume – LV end systolic volume / LV end diastolic volume) x 100%.

LVEF is an important prognostic variable and has been used to categorize patient groups into HFrEF, HFmrEF and HFpEF[166]. Such categorizations have had legacy implications for trial designs and outcomes, where the burden of evidence supports the use of established guideline-directed device and medication therapies primarily in patients with HFrEF, with the recent addition of recommendations for treatments such as sodium glucose co-transporter 2 (SGLT2) inhibitors in patients with more mildly impaired or preserved systolic function[2,167]. Patients with severely reduced LVEF tend to have higher resting intra-cardiopulmonary pressures than people with HFpEF whose pressures more often elevate with exertion[45,168-170]. LVEF, while sensitive to changes in cardiac pre-load and afterload, does not accurately reflect the complex interaction with diastolic function that occurs with left ventricular filling. Several studies have shown that LVEF correlates poorly with LV end-diastolic pressure measured at a single time point[171,172].

1.9.4 Lung function tests

Notwithstanding the potential for co-existing lung and cardiac disease, lung function tests in patients with advanced heart failure may resemble obstructive, restrictive or mixed lung disease[173-176]. Impaired forced vital capacity, total lung capacity and forced expiratory volume have been observed in patients with HF, particularly in the setting of secondary pulmonary hypertension[177]. As congestion occurs in the lungs or vascular remodelling develops in the setting of elevated left-sided cardiac and pulmonary pressures the parenchyma become stiffer and alveolar gas exchange is impaired. Increased left atrial pressures may lead to engorgement of the bronchial circulation, encroaching on the airways. Persistent pulmonary congestion can provoke bronchial hyperreactivity, accounting for the phenomenon described as “cardiac wheeze”. In the Acute Study of Clinical Effectiveness of Nesiritide and Decompensated Heart Failure (ASCEND-HF) trial, peak expiratory flow improved compared with baseline, along with dyspnoea as measured by a Likert scale, in patients after treatment was initiated, indicating that cardiac-related bronchial hyper-reactivity is a reversible target of decongestion[178,179]. Collectively, these maladaptations contribute to an increase in ventilatory demand (hyperventilation). Importantly, the hyperventilatory response to exertion is represented as an increase in breathing rate (frequency) rather than an increase in breathing depth (tidal volume)[180]. The main consequence of reduced lung compliance in patients with HF is an increased elastic load imposed on the respiratory muscles during inspiration. Patients with HF require larger swings in intrathoracic pressures to achieve a similar tidal volume compared with their healthy controls due to the marked reduction in lung compliance, a feature that seems to worsen with exercise[181,182]. The adaptive phenomenon of rapid, shallow breathing (increase in respiratory rate rather than volume) may have a protective effect of maintaining or

improving cardiac output during exertion by lessening negative inspiratory intrathoracic pressure and augmenting positive expiratory pressure[183-185]. Thoracic impedance, measured by implanted pacemaker leads in animal models, has demonstrated reductions in tidal volume of up to 68% compared with baseline when HF was induced through sustained rapid pacing[186]. Conversely, in a study of patients with HF who were administered sodium nitroprusside while undergoing RHC, reductions in PVR and PCWP were combined with increases in the ratio of tidal volume to inspiratory time, indicating an increase in ventilatory capacity. In this same cohort, changes in minute ventilation (tidal volume x respiratory rate) were correlated with change in PCWP ($r = 0.75$, $p<0.010$) and PVR ($r = -0.63$, $p<0.050$)[187]. Given such interaction between cardiac and pulmonary function, the potential to monitor respiratory status offers an important parameter for remote monitoring.

1.9.5 Natriuretic Peptides

The release of proBNP (brain natriuretic peptide) is triggered in response to ventricular, particularly left ventricular, wall stretch caused by plasma volume expansion or pressure overload[188-190]. proBNP is encoded by the NP precursor B (NPPB) gene[191]. Transcription of the NPPB gene leads to the production of preproBNP, a 134 amino acid proBNP hormone precursor, from which $proBNP_{1-108}$ is yielded following the removal of a 26 amino acid signal peptide. $proBNP_{1-108}$ undergoes proteolysis by proteases corin and furin to produce the biologically active BNP and its biologically inactive equivalent NT-proBNP[192,193]. NT-proBNP and BNP are rapidly released into the plasma within minutes of being synthesised providing a useful reflection of cardiac stress[194-197] and upon binding to natriuretic peptide receptors induce vasodilatation, natriuresis, diuresis, improved myocardial relaxation and anti-fibrotic

effect within the myocardium[198] to act as important counter-balancers of the deleterious effects of sodium retention, vasoconstriction and fluid retention that occur with activation of the renin-angiotensin-aldosterone and sympathetic nervous systems in HF. Atrial natriuretic peptide (ANP) is encoded by the Natriuretic Peptide Precursor A gene, transcription of which produces preproANP a 151 amino acid stored in atrial tissue as $proANP_{1-126}$. When $proANP_{1-126}$ is released, it undergoes rapid degradation to the active C-terminal ANP and an N-terminal prohormone of ANP[199]. Mid-regional pro-ANP (MR-proANP), is released in an equal ratio to ANP[199] and is more stable than the N- or C-terminal part[200] giving it relative advantage as a measure of both diagnosis and prognosis in HF. MR-proANP, NT-proBNP and BNP appear to have similar diagnostic and prognostic value[201-203].

The strength of correlation between natriuretic peptides and invasively measured haemodynamics has been variable, depending on the setting and patient cohort analysed. In patients with advanced HF, BNP and change in BNP correlated poorly with PCWP and change in PCWP[204]. In a separate cohort study of patients admitted to intensive care with a study entry criterion of >20mmHg, change in percentage BNP and change in percentage PCWP were highly correlated ($r = 0.79$, $p < 0.050$)[196]. Several factors limit the usefulness of natriuretic peptides for determining the presence or severity of congestion. As described, natriuretic peptides are released almost exclusively from cardiac tissue, but congestion, particularly tissue congestion is a systemic process making BNP and NT-proBNP indirect markers of the congested state[201,205]. There are a number of other conditions, other than HF, which also cause elevated wall stress without necessarily inducing fluid accumulation or redistribution such as atrial fibrillation, ischaemia, pulmonary embolism. Renal impairment and advanced age are also associated with elevated natriuretic peptides, while obesity can

reduce their concentrations. Age and renal function are important considerations given one-third of patients with HF have renal impairment[206] and the mean age of patients with HF is 78 years[3]. As only 25% of natriuretic peptide clearance is via the kidneys[207,208], the elevation in natriuretic peptides associated with chronic kidney disease cannot solely be accounted for by reduced filtration capacity and likely reflects a cardio-renal counter-regulatory response[209,210]. This is further supported by elevated natriuretic peptide concentration being of prognostic significance in patients with renal disease[207]. As the left ventricle is the pre-dominant source of natriuretic release, measured levels in right-sided HF may not adequately reflect severity of its impairment or consequences [211,212]. Lastly, there appears to be some intra-individual variability in natriuretic peptide levels that may affect the value of serial, trend measures of congestion[213]. Perhaps reflective of these limitations, the evidence to support the use of natriuretic peptides to reduce clinical endpoints such as hospitalization for HF or mortality is varied. The Guiding Evidence Based Therapy Using Biomarker Intensified Treatment in Heart Failure (GUIDE-IT) trial randomised patients with HFrEF to standard care or to NT-proBNP guided therapy with intensification of treatment to target a level <1000 pg/ml[214]. Compared with standard care, there was no difference in the composite primary outcome of cardiovascular mortality or hospitalization for HF with NT-proBNP guided treatment and no mean difference in loop diuretics doses were observed[214]. A more personalized approach is to consider the percentage change in natriuretic peptide, a >30% change being proposed as clinically meaningful in terms of reducing mortality[205,215].

1.9.6 Haematocrit

Haemoconcentration, as indicated by relative increases in haemoglobin or haematocrit following treatment for congestion, has attracted interest as of a marker of

decongestion[216,217]. Studies correlating plasma volume by radio-labelled iodine tracer methods and estimated plasma volume by calculation including haematocrit and weight, have varied results. Moderate correlation has been reported between actual and estimated plasma volumes in patients with HF ($r = 0.29$, $p = 0.030$) with stronger correlation in healthy controls ($r = 0.71$, $P<0.001$)[31,218,219]. Patients admitted with decompensated HF who achieved haemoconcentration (defined as an absolute increase in haematocrit ≥3%) in the Efficacy of Vasopressin Antagonism in Heart Failure Outcome Study with Tolvaptan (EVEREST) trial had substantially greater weight loss and reduction in natriuretic peptides with decongestion and improved mortality compared with people who did not haemoconcentrate[220], a finding that has been reproduced in several of cohorts of patients with HF[221]. It is unclear whether early or late haemoconcentration during decongestion confers a survival advantage as conflicting benefits on mortality have been reported [222,223].

1.9.7 Physical signs

1.9.7.1 Third heart sound

The third heart sound, or S3, is a low frequency vibration heard in early diastole shortly after the second heart sound, often described as a gallop rhythm[224]. The presence of a S3, compared to its absence, has been associated with elevated filling pressures depending on the population studied. In one study of 52 patients referred for transplant evaluation, 29 people had an audible S3, of whom 25 (86%) had a PCWP >18mmHg. However, 12 of 37 (32%) people with a PCWP >18mmHg did not have a S3. Sensitivity of an auscultated S3 for a PCWP >18mmHg was 68%[225]. In the larger ESCAPE trial, the sensitivity for a higher threshold PCWP >22mmHg was consistent with the aforementioned study (62%) but with a

substantially lower specificity (32%). In that study 123 of 192 (64.1%) patients were reported to have a S3 at baseline. In a study of 1281 patients with valvular heart disease, the presence of S3 was common in patients with mitral regurgitation but did not reflect elevated filling pressures (PCWP with S3 = 18.9 versus PCWP without S3 = 17.4, p = 0.290). S3 was uncommon in aortic stenosis but was associated with higher PCWP if present compared with its absence (18.6mmHg vs 12.1mmHg, p <0.001)[226]. While the strength of the relationship between S3 and filling pressures may vary according to the patient population, there are also additional factors such as environmental noise, adiposity, heart rate and atrial fibrillation that may make its auscultation more challenging. High degrees of inter-rater variability in detecting S3 have been observed, with Kappa statistic values as low as 0.18 (95%CI 0.13 – 0.24) reported[227]. Notwithstanding some of these limitations, when detected, the presence of a S3 has been strongly associated with death from HF ("pump failure") in patients with symptomatic HF [adjusted relative risk (RR) = 1.40 (95%CI 1.14 – 1.71), p <0.005][228] and as a marker of developing HF in people with asymptomatic left ventricular dysfunction [adjusted RR = 1.38, 95%CI 1.09 – 1.73, p = 0.007][229].

1.9.7.2 Jugular Venous Pressure

The internal jugular vein is preferred to the external jugular for the estimation of jugular venous pressure (JVP) as the latter is valved and not directly in line with the superior vena cava or atrium. Venous pressure, measured in centimetres of water (cmH_2O), is the vertical distance from the top of the venous pulsation to the angle of Louis on the sternum. A distance of ≥4cm is considered elevated. Estimations at the bedside in cm require conversion to mmHg for equivalence with invasive haemodynamics (1.36 cmH_2O = 1.0

mmHg)[93]. The JVP is identifiable from the carotid pulsation by having two undulating peaks and troughs, by not being palpable, but instead being possible to obliterate, by backfilling up when compressed and by falling more prominently with inspiration. Hepatojugular reflux can be elicited by pressing on the right upper quadrant and observing for elevation in the JVP. The JVP waveforms are in line with the waveforms described above for invasive measurement of the right atrium.

In the ESCAPE trial, 82% of patients with an clinically estimated low right atrial pressure (<8mmHg) had a correspondingly low pressure on RHC. When the threshold was set at >12mmHg, 70% of those with a clinical estimation at that level also were found to have a right atrial pressure >12mmHg on RHC. There was some relationship between JVP elevation and PCWP in the same cohort. In a multi-variable model, only JVP ≥12mmHg was associated with PCWP >22mmHg (OR 3.3, 95%CI 1.8 – 6.1)[230]. In a separate cohort of patients with advanced HF, JVP had modest sensitivity (57%) for detecting PCWP ≥18mmHg which was augmented to 81% when combined with the presence of hepatojugular reflux[225]. JVP elevation was not often observed in patients enrolled in clinical trials, reported as being evident in 9.7% - 11.3% participants at baseline[13,228]. It has a strong association with death from HF in both patients with symptomatic HFrEF (RR 1.37, 95%CI 1.07 – 1.75, p <0.005) and of death or development of HF in patients with asymptomatic left ventricular dysfunction (RR 1.54, 95%CI 1.11 – 2.12, p = 0.010) [228,229].

1.9.7.3 Peripheral Oedema

The development of peripheral oedema in HF, including ascites, is the manifestation of tissue congestion with fluid accumulation in the interstitium of peripheral tissues. It is the most

observed sign of congestion in contemporary trial cohorts of patients with chronic ambulatory HF, reported in 1193 of 8,399 (14.2%) patients enrolled in the PARADIGM-HF trial[13]. Oedema may be the result of other conditions, including venous insufficiency, obesity, lymphoedema, nephrotic syndrome or cirrhosis. While peripheral oedema may occur with isolated right HF or mixed left and right HF, it is fundamentally related to elevated right sided pressures as demonstrated in the ESCAPE trial where the proportion of patients with peripheral oedema progressively increased as the ratio of right atrial pressure to PCWP increased (RAP:PCWP ratio tertile 1 = 14% with oedema vs RAP:PCWP ratio tertile 3 = 62% with oedema, $p<0.001$)[231]. In another haemodynamic study, the combination of JVP elevation and peripheral oedema was present in 21 of 28 people (75%) with a right atrial pressure $\geq$10mmHg[232]. However, among patients with advanced HF, the presence of oedema has been shown to have a broad range of sensitivity and specificity for elevated left sided pressures at different thresholds (sensitivity for PCWP >22 mmHg = 41%, specificity = 66% and sensitivity for PCWP > 18mmHg = 27%, specificity = 87%)[225,230]. Another early haemodynamic study of 50 patients undergoing RHC, reported none of 10 patients with peripheral oedema had a PCWP >22mmHg[232]. It can be therefore deduced that the development of peripheral oedema is often a relatively late feature in the natural history of left-sided HF decompensation when compared with symptoms and signs such as dyspnoea or pulmonary rales.

1.9.7.4 Pulmonary rales

Due to enhanced lymphatic drainage in chronic HF pulmonary rales have been found to be absent in up to 63% of people with a PCWP >22mmHg[230]. It has been reported to have a

range of prevalence in people with chronic ambulatory HF, present in approximately 8% - 26%[15,233]. In patients without a diagnosis, the presence of rales on presentation was associated with OR 2.12 (95%CI 1.31 – 3.75) of a subsequent diagnosis of HF. When present in patients with advanced HF, rales were associated with PCWP ≥22mmHg in all patients (n = 8) [234] and a 100% positive predictive value for PCWP >18mmHg (n = 9) [225] in two small, early haemodynamic studies.

1.9.8 Physical symptoms

1.9.8.1 Dyspnoea

Dyspnoea is the predominant symptom of HF and congestion with over 90% of patients enrolled in HF registries reporting its presence[235,236]. It is broadly considered that elevations in intra-cardiopulmonary filling pressures either at rest or on exertion are responsible for pulmonary functional derangements (interstitial oedema, vascular engorgement, reduced compliance or increased airways reactivity) that account for the breathlessness encountered in HF, along with the potential for co-existing intrinsic pulmonary disease[168,169,237-239]. However, due to adaptations in venous capacitance and lymphatic drainage with chronically elevated pressures, patients with persistently higher PCWP may not experience the same intensity of clinical dyspnoea or radiographic congestions as someone with new onset HF[232,240]. Despite playing a central role in the experience of people with HF, there is no one universally agreed upon standard measure of breathlessness in clinical trials or practice [241]. A Likert-based or visual analogue approach to assessing dyspnoea or its functional impact has been proposed as an appropriate approach regardless of the scale used, while physician-interpreted grades of limitation (such as assigning NYHA class, where dyspnoea is a major contributor to limitation) are frequently subject to inter-rater variability[242,243]. While

resolution of dyspnoea should be a goal of treatment in decompensated patients with HF, it remains present in up to 43% of patients at discharge[244]. However, the severity of dyspnoea at discharge or its change (improvement post-treatment) from admission is often not captured in data from sources such as registries. With appropriate treatment, acute dyspnoea has been reported to improve within 6 hours of admission and treatment[245], and may be the clinical feature that precedes resolution of other physical signs such as rales, peripheral oedema or jugular venous distension[17]. In the EVEREST trial, 43% of patients admitted with decompensated HF had achieved a relief of symptoms including dyspnoea (EVEREST congestion score = 0). However, even with the resolution of symptoms, 35.6% of patients either died or were readmitted within a median follow-up of 9.9 months, an observation that supports concerns that the absence of symptoms may mask the underlying haemodynamic alterations that lead to a symptomatic decompensation or indeed persist after its perceived resolution. The extended breathlessness symptoms of orthopnoea and bendopnoea as discussed below.

1.9.8.2 Orthopnoea

Breathlessness on positioning supine, otherwise known as orthopnoea, results from redistribution of fluid from venous reserves such as the splanchnic system or lower limbs with an additional 250 mls being returned to the heart and lungs. Pulmonary venous and capillary pressures rise which under conditions of greater hydrostatic force can induce translocation of fluid into the interstitium, reduce pulmonary compliance and cause dyspnoea. The severity of orthopnoea may reflect the rapidity of relative elevation in intracardiac pressures as well as the absolute value[246]. Orthopnoea is a frequent symptom

reported at the point of admission for HF decompensation and was present in 77.1% of patients on enrolment into the ASCEND-HF trial [28,179]. An early study examining the relationship between orthopnoea and haemodynamics in patients with advanced HF, demonstrated that orthopnoea was common (present in 39 of 50 study participants) and all of these 39 patients were among the 43 people who had a PCWP $\geq$ 22mmHg. None of the seven people who had lower PCWP values reported orthopnea[232]. However, these findings have not been replicated in all other studies, with orthopnoea having sensitivity of 66% and specificity of 47% in identifying patients undergoing transplant assessment who had a PCWP >20 mmHg[247]. In a sub-analysis of the ESCAPE trial, orthopnoea was poorly related to a PCWP $\geq$22mmHg but was strongly associated with higher PCWP thresholds in multi-variable models (OR 3.60, 95%CI 1.02 – 12.80, p<0.050 for a PCWP >30mmHg)[230]. People with ambulatory HF and persistence of orthopnoea despite treatment have been observed to have a 49% higher risk of hospitalization for HF than patients without orthopnoea[248]. Given its association with prognostically important outcomes and correlation with haemodynamic alterations of congestion, orthopnoea has been incorporated into several congestion scores, including the EVEREST congestion score that was analysed in the three study cohorts of my PhD project[17,249-251].

1.9.8.3 Bendopnoea

Bendopnoea is shortness of breath on bending forward. Often a patient with HF will report this symptom occurring during a simple activity such as tying a shoelace. Bendopnoea has been shown to correlate with higher right atrial, pulmonary and PCWP filling pressures and greater symptom burden as evidenced by higher proportions of patients with NYHA class IV

symptoms, dyspnoea on exertion, bloating and oedema having bendopnoea compared with those without bendopnea[25,252,253]. The relationship between bendopnoea and mortality has not been widely described. In one study of 250 patients admitted with HF, bendopnoea was associated with a 39% relative risk increase in 6-month all-cause mortality in univariate analysis but this association was not present after adjustment in a multi-variable model[254].

1.9.9 Body weight

Monitoring weight remains central to HF management programmes[2] and has been included in telemedicine strategies to reduce HF related admission and mortality[255].

Congestion as a consequence of sodium and water retention is often associated with an increase in body weight. 1 litre of retained water should equate to a 1kg rise in body weight. However, owing to different mechanisms such as volume redistribution to account for decompensation in HF, changes in weight have been shown to have modest predictive value (Receiver Operating Characteristic (ROC) curve, Area Under Curve (AUC) = 0.64, 95%CI 0.54 – 0.77) for HF deterioration in ambulatory patients[27]. In the ASCEND-HF trial, the median changes in weight were -1.0kg (-2.1 to 0.0) at 24 hours and -2.3kg (-5.0 to -0.7) at day 10 / discharge. Change in weight was weakly correlated with urine output (r = -0.38, <0.001) and dyspnea relief as graded on a Likert scale (r = -0.09, p <0.001)[28]. Similar degrees of median weight loss were observed in the EVEREST trial [-2.2kg (-4.1 to -0.9)] [17]. In a study of 55 patients with decompensated HF and serial invasive studies, a discordance between change in weight and haemodynamics was evident. There was a clinically notable change in weight (-3.4 $\pm$ 7.1kg) and change in PCWP (-5 $\pm$ 10mmHg) and RAP (-6 $\pm$ 8mmHg) between study visits. However, when change in weight was correlated with change in PCWP (r = 0.01, p =

0.920) and change in right atrial pressure (r = 0.11, p = 0.450), no relationship between the measures was identified [256].

1.9.10 Congestion Scores

Using data collected during several randomised controlled trials of patients with decompensated HF, investigators have derived congestion scores as clinical prediction tools to predict future clinical events. The individual parameters comprising different scores are detailed by study in **Table 1-2**. There is a consistent association between higher congestion score and mortality across studies and analyses. In the EVEREST trial, the relative hazard of 30-day mortality was increased by 34% per 1 point increase in the composite score (HR 1.34, 95%CI 1.14 – 1.58)[17]. In the ASCEND-HF trial, the adjusted odds ratio for 30-day all-cause mortality for patients with a congestion score above the median score of 4 points, compared with people with a score below 4, was 1.78 (95% Cl 1.32–2.40, p < 0.001)[249]. Using data in the OPTIMIZE-HF registry on 24,724 patients admitted with HF, a 3-point increase in the composite congestion score was associated with a 6% increase in mortality (HR 1.06, 95%CI 1.03 – 1.09)[250]. While the relationship with increasing congestion score and mortality is clear from these data, no studies have correlated the composite scores with invasive haemodynamics or compared them with each other as means to monitor changes in fluid status

Table 1-2 Clinical congestion scores

	Dyspnea	Orthopnea	Fatigue	JVP (cm)	Rales	Oedema	NT-proBNP
EVEREST[17]	0 – none 1 – seldom 2 – frequent 3 – continuous	0 – none 1 – seldom 2 – frequent 3 – continuous	0 – none 1 – seldom 2 – frequent 3 – continuous	0 – ≤6 1 – 6 to 9 2 – 10 to 15 3 – ≥15	0 – none 1 – bases 2 – to <50% 3 – to >50%	0 – trace 1 – slight 2 – moderate 3 – marked	—
ASCEND-HF[249]	—	0 – No 2 – Yes	—	—	—	0 – none 1 – shin 2 – knee 3 – sacrum	1 – <1893 2 – 1893 to <5262 3 – >5262
CARRESS-HF / DOSE-HF[251]	—	0 – Mild oedema, no orthopnea	—	—	—	See orthopnea	—

		1 – Moderate oedema, no orthopnea 2 – Severe oedema OR orthopnea 3 – Moderate oedema AND orthopnea 4 – Severe oedema AND orthopnea					
OPTIMIZE-HF[250]	0 – none 2 – on exertion 3 – at rest	0 – none 2 – yes	0 – none 2 – yes	0 – not elevated / ≤6 1 – unknown / 6 to 9	0 – none 1 – unknown / <1/3	0 – Trace 1 – unknown / 1 plus 2 – 2 plus	———

				2 – 10 to 15 3 – >15	2 – ≥1/3	3 – ≥3 plus	

2. CHAPTER TWO. Meta-analysis of randomized controlled trials examining the efficacy of implantable haemodynamic monitoring in heart failure across ranges of ejection fraction.

2.1 Introduction

Remote monitoring using implanted devices can provide useful information about the natural history of congestion leading to decompensation in people with HF. Early identification of increasing cardiopulmonary pressures and intervention to reduce these could decrease the risk of subsequent HF hospitalization. Based on the CHAMPION trial, the CardioMEMS implantable pulmonary artery pressure monitor received a class IIb recommendation to reduce HF hospitalizations in the 2021 ESC HF guidelines[2]. In the haemodynamic-GUIDed management of Heart Failure (GUIDE-HF) trial, the largest randomised controlled trial (RCT) to compare implantable haemodynamic monitoring (IHM) with standard care, IHM-guided care did not reduce HF hospitalizations overall, but sensitivity analyses suggested a modest benefit before the COVID-19 pandemic had an impact on patient management[54].

No previous meta-analysis has included data from both the GUIDE-HF and the Left Atrial Pressure Monitoring to Optimize Heart Failure Therapy Study (LAPTOP-HF), the latter of which was an international randomised controlled trial that reported its findings in 2016[60] (**Table 2-1**). Additionally, despite IHM randomised trials recruiting patients across a range of EF no meta-analysis reported the effect of IHM on the reduction of HF hospitalizations and related events in subgroups of patients with heart failure with a preserved ejection fraction

(HFpEF) or heart failure with a reduced ejection fraction (HFrEF). This type of monitoring is of particular interest in patients with HFpEF, in whom evidence-based treatment options are limited. Therefore, in this meta-analysis of all randomised trials using IHM, I investigated whether treatment guided by such monitoring reduced the risk of total (first and recurrent) HF hospitalizations, total worsening HF events [HF hospitalization and emergency department (ED) and urgent clinic visit for intravenous (IV) HF therapy] and all-cause mortality, when compared with standard care, in patients with HF across a range of EFs.

Table 2-1 Randomised controlled trials of IHM-guided HF management compared to standard care

Trial	First Author and Year	Design, Country	Primary Efficacy Endpoint	Numbers Enrolled	Ejection Fraction	NYHA Class	Previous HF Event	Follow-up
COMPASS-HF[48]	Bourge et al, 2008	Single blind*, multi-centre, RCT USA	HF hospitalization and ED and urgent clinic visit for IV therapy (included hypovolaemic events)	274	No EF Inclusion criterion	III-IV	≤6 months (or ED visit)	6 months
CHAMPION[50]	Abraham et al, 2011	Single blind*, multi-centre, RCT USA	HF hospitalization	550	No EF inclusion criterion	III	≤12 months	6 months
REDUCE-HF[52]	Adamson et al, 2011	Single blind*, multi-centre, RCT USA	HF hospitalization and ED and urgent clinic visit for IV therapy	400	No EF inclusion criterion	II-III	≤12 months	12 months
LAPTOP-HF[60]	Abraham et al, 2016	Multi-centre, RCT (no blinding) USA and New Zealand	HF hospitalization and complications from HF therapy	486	No EF inclusion criterion	III	≤12 months (or BNP ≥400 pg/ml or NT-ProBNP ≥1,500 pg/ml)	12 months
GUIDE-HF[54]	Lindenfeld et al, 2021	Single blind*, multi-centre, RCT	All-cause mortality and HF hospitalization and ED and urgent clinic visit for IV therapy	1000	No EF inclusion criterion	II – IV	≤12 months (or BNP ≥250 pg/ml or	12 months

	USA and Canada	NT-ProBNP ≥1,000 pg/ml)

*****Patients but not investigators were blinded to haemodynamic data

BNP = brain natriuretic peptide; ED = emergency department; EF = ejection fraction; HF = heart failure; IHM = implantable haemodynamic monitor; IV = intravenous; NT-ProBNP = N- terminal pro B-type natriuretic peptide; NYHA = New York heart association; RCT = randomised controlled trial; USA = United States of America

2.2 Methods

2.2.1 Search Strategy and Data Extraction

A systematic review of RCTs in patients with HF was performed, comparing IHM-guided care versus standard therapy. This meta-analysis was registered on PROSPERO, CRD42021253905. The Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines were followed to conduct the literature search, data extraction and reporting. Bias was assessed using the Revised Cochrane risk-of-bias tool for randomised trials (RoB 2)[257] (**Table 2-2**).

Table 2-2. Revised Cochrane risk-of-bias tool for randomised trials (RoB 2)

Domain	COMPASS-HF	CHAMPION	REDUCE-HF	LAPTOP-HF	GUIDE-HF
1- Randomisation					
2- Deviations from intended interventions					
3- Missing outcome data					
4- Outcome measurement					
5- Selective reporting					
Overall					

 Low level of concern

 High level of concern

 Some concern

Searches were performed on public databases (PubMed and Ovid Medline) between May 1st 2020 and September 5th 2022 using the terms “heart failure AND implantable AND haemodynamic monitoring” and “left atrial pressure AND heart failure AND monitoring” and “pulmonary artery pressure monitoring AND heart failure”. All studies published up until September 5th 2022 were eligible. No restriction was placed on study size, language or country of publication. Titles and abstracts were screened based on pre-specified inclusion criteria using the PICOS framework:

- Population: patients with HF
- Intervention: IHM-guided care
- Comparator: Standard care
- Outcomes of interest:
    - HF hospitalization
    - Worsening HF events (HF hospitalization and ED and urgent clinic visits for IV HF therapy)
    - All-cause mortality
    - All-cause mortality and HF hospitalization
    - All-cause mortality and worsening HF events
- Study design: RCTs

Full text articles of original trial reports and published articles with retrospective analyses of the RCTs were included. Data presented at conferences were included if the presentation was available and verifiable by the researchers. Hazard ratios (HR) and incidence-rate ratios (IRRs) for endpoints were recorded. IRR are approximations of HRs and were included as the effect estimate if HRs were not available as has previously been reported[258-260]. If either HR or IRR were not reported in the literature, the IRR was calculated using event numbers and

study cohort time-at-risk. 95% CIs were calculated if only a p value and effect estimate were reported[261]. Numbers of patients in EF subgroups and their numbers of events were calculated from available data where necessary. Two researchers (Dr James P Curtain and Dr Matthew MY Lee) independently extracted and analysed the data. Results were compared and differences resolved by consensus with opinion from a third author (Prof Pardeep S Jhund). If data were not available, the original study authors were contacted and data were requested.

2.2.2 Statistical Analysis

I performed the statistical analyses using Stata 17 (College Station, Texas, USA). As the trials were of varying size and investigated three devices across different decades I used a random effects [DerSimonian and Laird (D+L)][262] model so that differences in the study designs and cohorts would be accounted for within the analysis. I performed sensitivity analyses of each meta-analysis using fixed-effects models. Only the result of the fixed effect model in patients with HFpEF is reported, as the other fixed effect analyses were consistent with the reported random effects models. I^2 statistic for percentage heterogeneity was computed with corresponding *p* values. Forest plots graphically report the pooled effect size estimates, the degree of heterogeneity and the weighted contribution each study made to the analyses. All outcomes were examined in total events (first and recurrent) analyses.

2.2.3 Definitions of HFpEF and HFrEF

HFpEF was defined as HF with an LVEF≥50% in keeping with the 2021 ESC Heart Failure guidelines[2] and the recently proposed universal definition of HF[1]. HFrEF was defined as HF

with an EF<50%, with the inclusion of patients with mildly reduced EF (HFmrEF, EF 41-49%) as well as patients with an EF≤40%. There were insufficient data available to further subclassify the trial cohorts into a HFmrEF subgroup. Only COMPASS-HF pre-specified an analysis of patients with an EF≥50%. While EF was not an inclusion criterion for the REDUCE-HF trial, patients included in that trial had severely impaired systolic function with a mean (± standard deviation) EF of 23% ± 7.[53] Patients from the REDUCE-HF trial were therefore included in the HFrEF (EF<50%) analysis. Similarly, patients from LAPTOP-HF in whom the mean EF was 30% ± 15[263], were included in the HFrEF (EF<50%) analysis.

2.2.4 Efficacy endpoints

The primary efficacy endpoints for each of the included trials were examined in total (first and recurrent) event analyses comparing the effect of IHM-guided care with standard care alone. These endpoints were as follows;

- COMPASS-HF and REDUCE-HF: total worsening HF events. HF hospitalizations for less than 24 hours were included in the composite endpoint in REDUCE-HF.
- LAPTOP-HF: total HF hospitalization and complications of HF treatment such as hypotension and acute renal failure.
- CHAMPION: total HF hospitalization.
- GUIDE-HF: all-cause mortality and total worsening HF events.

Recurrent events were analysed in a negative binomial regression model in COMPASS-HF and an Andresen-Gill model in CHAMPION, REDUCE-HF, LAPTOP-HF and GUIDE-HF. As these methods yield very similar results in simulations[264] and trial datasets[265] they were used in the meta-analysis. Meta-analysis was performed for *(i)* total HF hospitalizations and *(ii)* total

worsening HF events (HF hospitalization and ED visit and urgent clinic visit for IV HF therapy) *(iii)* all-cause mortality *(iv)* all-cause mortality and total HF hospitalizations and *(v)* all-cause mortality and total worsening HF events. Only hospitalizations for greater than 24 hours in REDUCE-HF were included in the total HF hospitalization analysis [*(i)* above)]. All-cause mortality data from COMPASS-HF, CHAMPION, REDUCE-HF and GUIDE-HF were pooled. The GUIDE-HF main trial results were published in 2021, followed by an analysis examining the impact of the COVID-19 pandemic on that trial's event rates[266]. I performed a sensitivity analysis examining the rate of HF events including the pre-COVID event rates and the results from the other four included trials.

2.2.5 Ethical approval

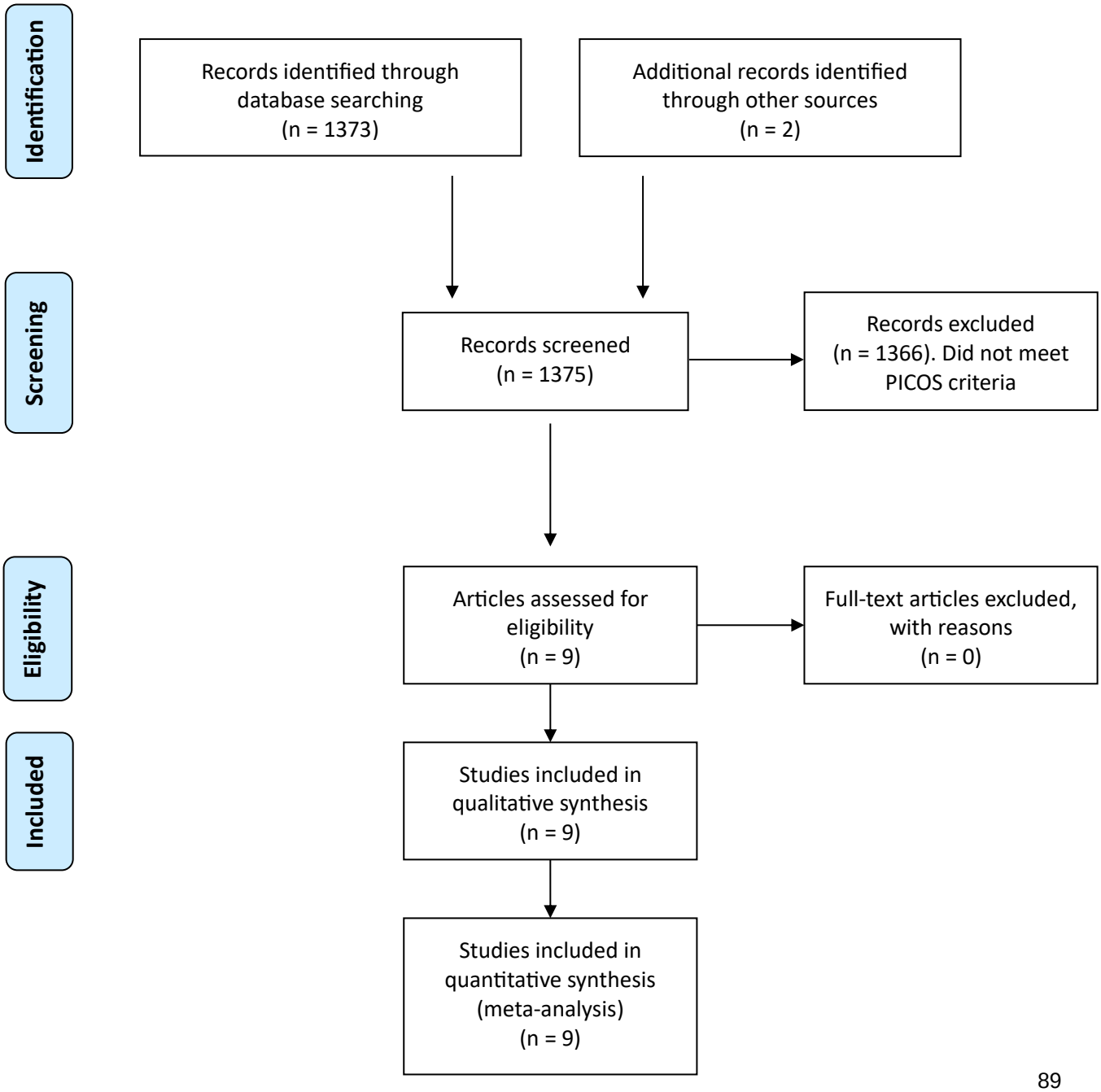
All trials were approved by a local ethics committee and complied with the Declaration of Helsinki. Patients provided written informed consent to participate in the studies.

2.3 Results

2.3.1 Literature review and search strategy

1,373 articles were identified by searching electronic databases. Two further articles[263,267] were found by hand searching references and internet searches. A PRISMA flow chart outlines the search process and identification of relevant articles (**Figure 2-1**).

Figure 2-1 PRISMA flow diagram of source articles for the meta-analysis



Five RCTs were identified (**Table 2-1**); COMPASS-HF, CHAMPION, REDUCE-HF, LAPTOP-HF and GUIDE-HF. The 18-month results for the CHAMPION trial were used in this meta-analysis[51]. The HR for HF hospitalization at one year was reported for 455 of the 486 randomised in LAPTOP-HF by the lead investigator at the annual meeting of the Heart Failure Association of the European Society of Cardiology in 2017[267].

2.3.2 Trial characteristics

COMPASS-HF, CHAMPION and REDUCE-HF were conducted in the United States of America (USA). LAPTOP-HF was conducted in the USA and New Zealand. GUIDE-HF was conducted in the USA and Canada. The COMPASS-HF and REDUCE-HF studies evaluated the Chronicle pressure sensor. The CardioMEMS device was investigated in CHAMPION and GUIDE-HF. The HeartPOD device was investigated in LAPTOP-HF. The main trial characteristics are summarized in **Table 2-1**.

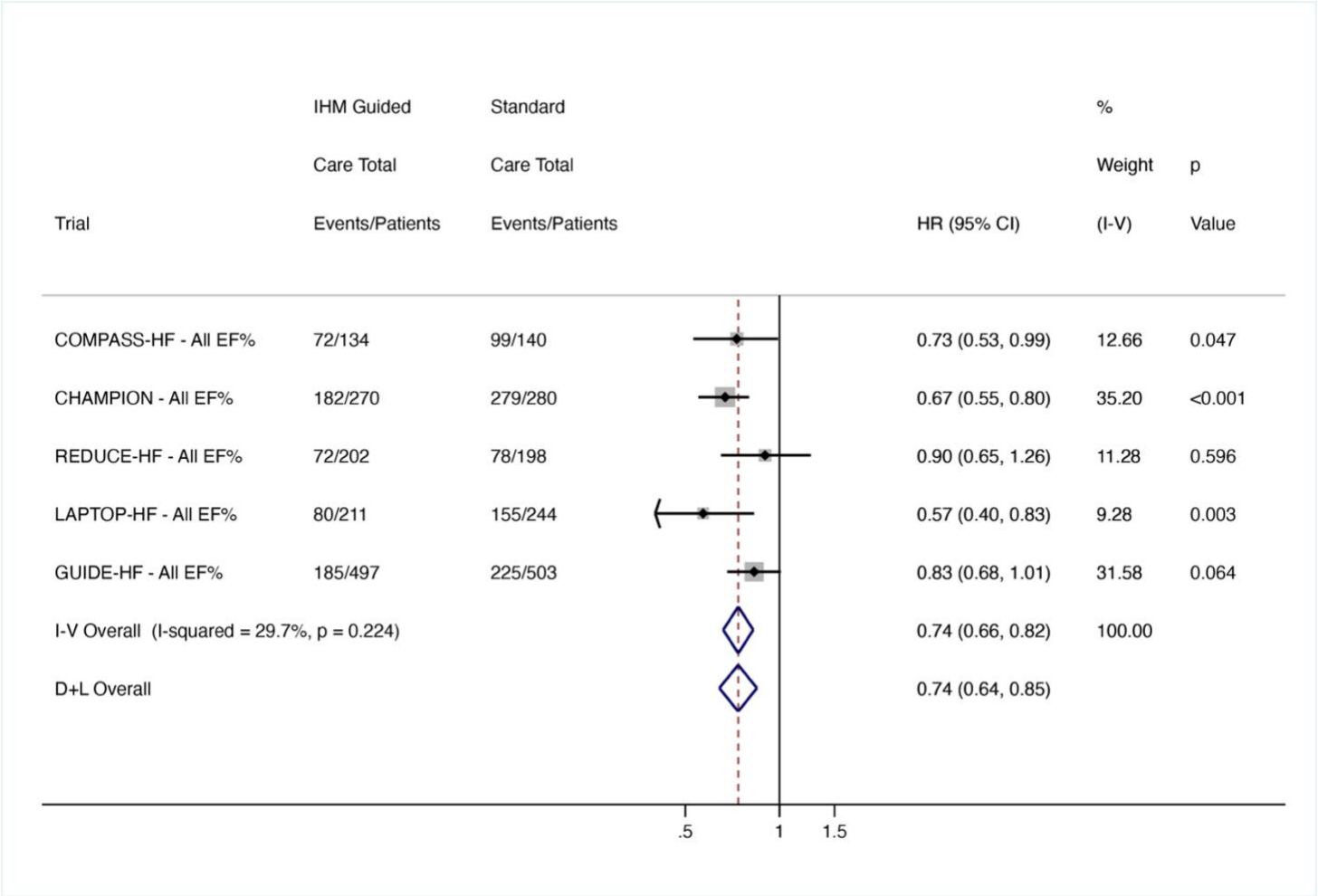
All participants underwent implantation of haemodynamic monitors and were randomised to receive HF care guided by haemodynamic data or receive standard care. COMPASS-HF, CHAMPION, REDUCE-HF and GUIDE-HF were single-blind studies where investigators, but not patients, had access to the treatment group haemodynamic data. Patients were unaware of their randomised assignment groups in these four trials. LAPTOP-HF had no blinding (ie patients and investigators were aware of the intervention assignment groups).

2.3.3 Patients with HF regardless of EF

Total HF hospitalizations: There were 591 hospitalizations in 1,314 patients receiving IHM-guided care compared with 836 events in 1,365 standard care patients. HF hospitalizations

were reduced in the IHM-guided care arm by 26% [HR 0.74, 95% CI 0.64 – 0.85; low heterogeneity (I^2 29.7%)] (**Figure 2-2**).

Figure 2-2 Total (first and recurrent) HF hospitalizations in all patients regardless of EF

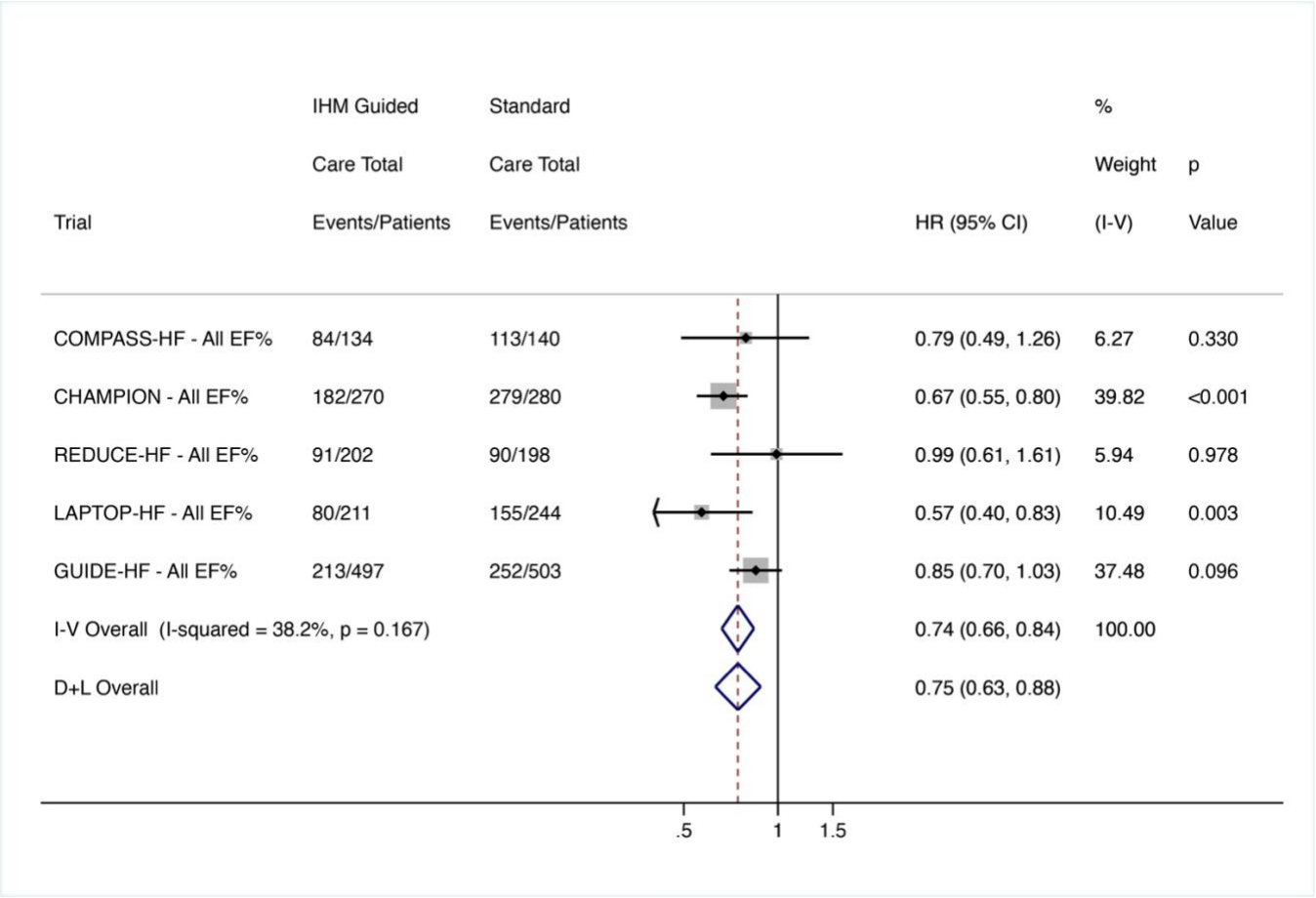


D+L = DerSimonian & Laird; EF = ejection fraction; HF = heart failure; HR = hazard ratio, IHM = implantable haemodynamic monitor; IRR = incidence rate ratio, I-V = inverse-variance.

*Recurrent event effect estimates include HRs for CHAMPION, LAPTOP-HF and GUIDE-HF and IRR for COMPASS-HF and REDUCE-HF

Total worsening HF events: There were 650 composite outcome events in 1,314 patients receiving IHM-guided care and 889 events in 1,365 standard care patients. IHM-guided care reduced total worsening HF events by 26% [HR 0.75, 95% CI 0.63 – 0.88; low heterogeneity (I^2 38.2%)] (**Figure 2-3)**. In a sensitivity analysis of pre-COVID-19 event rates in the GUIDE-HF trial, IHM-guided care reduced HF events by 29% [HR 0.71, 95%CI 0.63 – 0.81; low heterogeneity I^2 2.9%].

Figure 2-3 Total (first and recurrent) worsening HF events (HF hospitalization and ED and urgent clinic visit for IV HF therapy) in all patients regardless of EF

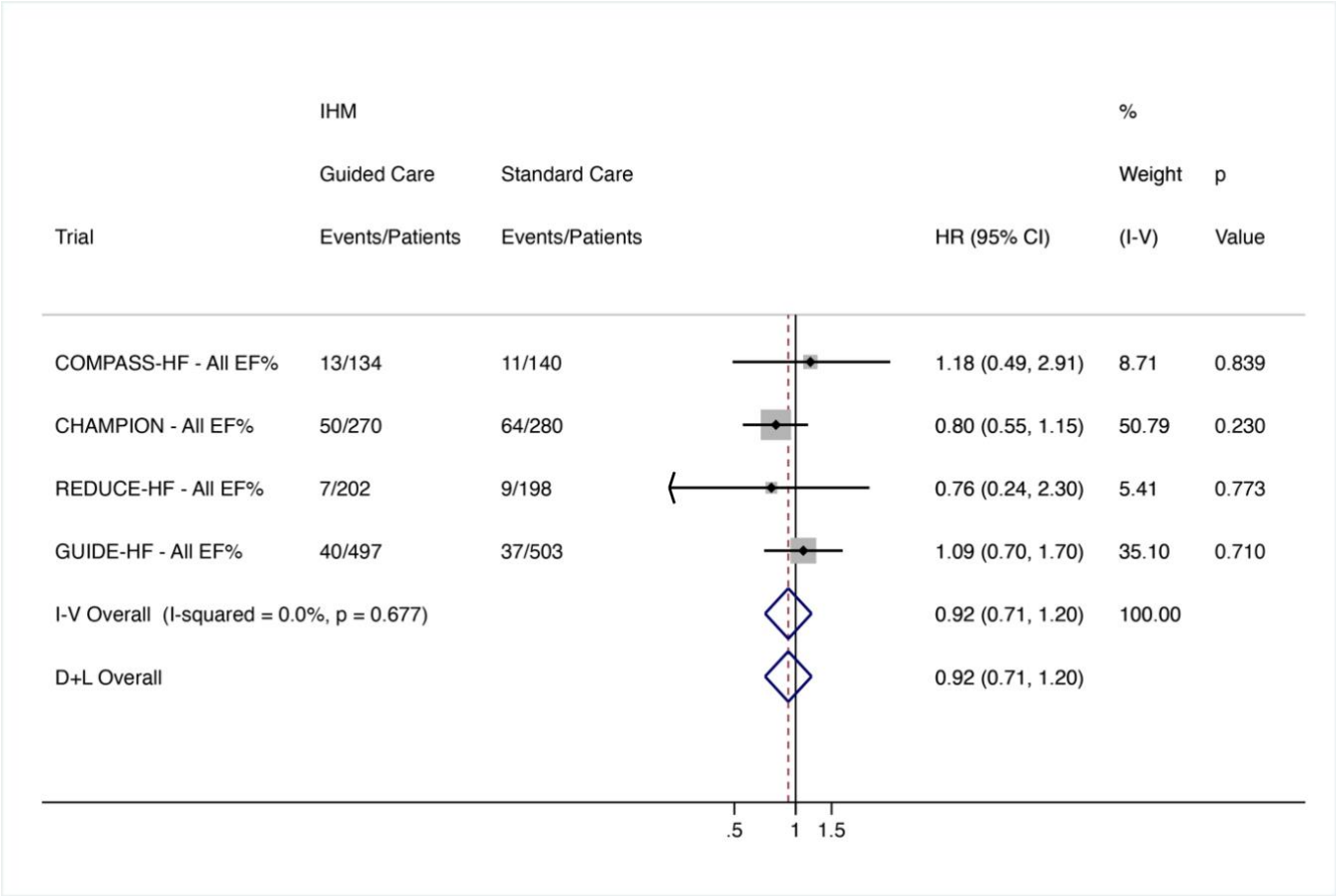


D+L = DerSimonian & Laird, ED = emergency department, EF = ejection fraction, HF = heart failure, HR = hazard ratio, IHM = implantable haemodynamic monitor, IRR = incidence rate ratio, IV = intravenous, I-V = inverse-variance

* Recurrent event effect estimates include HRs for CHAMPION, REDUCE-HF, LAPTOP-HF and GUIDE-HF and IRR for COMPASS-HF.

All-Cause Mortality: Mortality was reported in the COMPASS-HF, CHAMPION, REDUCE-HF and GUIDE-HF trials. 110/1,103 (10.0%) patients in the IHM-guided care arm died compared to 121/1,121 (10.8%) receiving standard care. IHM-guided care did not reduce all-cause mortality [HR 0.92, 95% CI 0.71 – 1.20; low heterogeneity (I^2 0%)] (**Figure 2-4**).

Figure 2-4 All-cause mortality in all patients regardless of EF for (COMPASS-HF, CHAMPION, REDUCE-HF and GUIDE-HF)

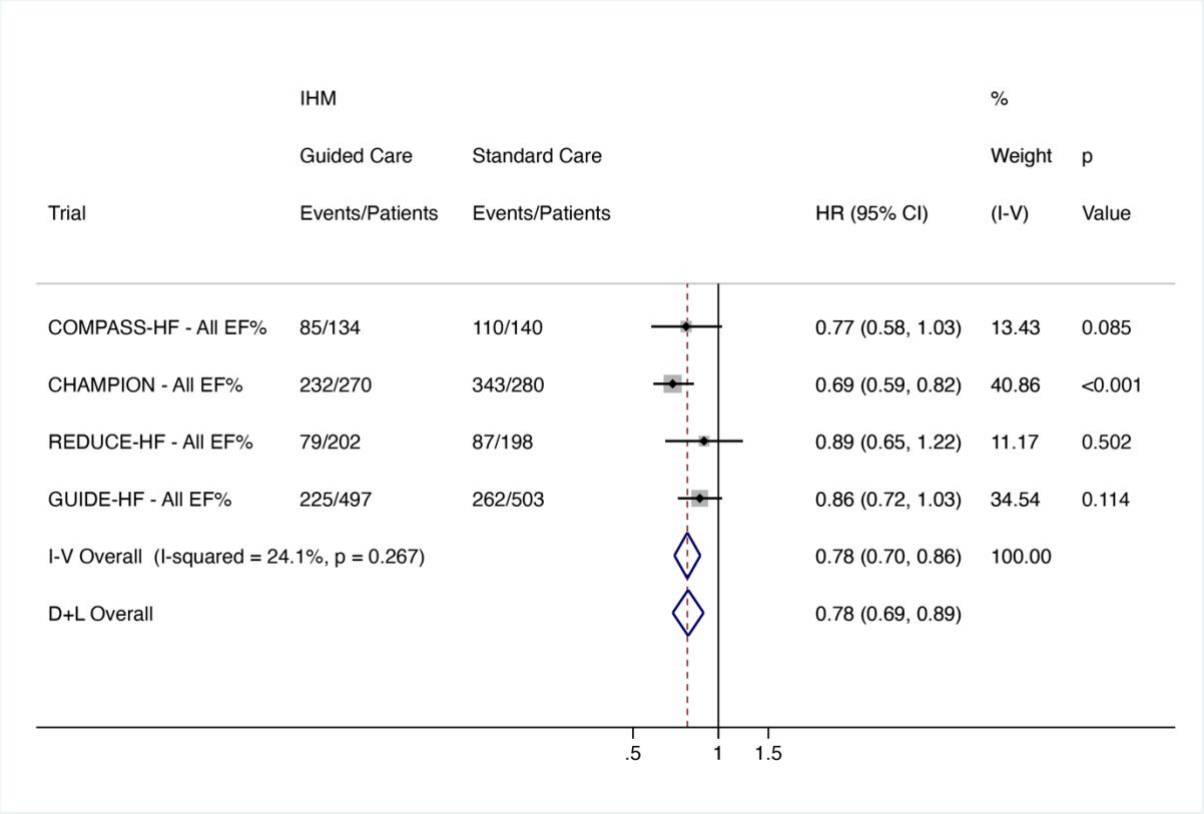


D+L = DerSimonian & Laird, EF = ejection fraction, HF = heart failure, HR = hazard ratio, IHM = implantable haemodynamic monitor, I-V = inverse-variance

*Recurrent event effect estimates include HRs for CHAMPION and GUIDE-HF and IRR for COMPASS-HF and REDUCE-HF.

All-Cause Mortality and total HF hospitalization: Data were available from COMPASS-HF, CHAMPION, REDUCE-HF and GUIDE-HF. 621 events in 1,103 patients occurred in the IHM arm and 802 events occurred in 1,121 standard care patients. IHM-guided care, compared to standard care, reduced all-cause mortality and total HF hospitalization by 22% [HR 0.78, 95% CI 0.69 – 0.89; low heterogeneity (I^2 24.1%)] (**Figure 2-5**).

Figure 2-5 Total (first and recurrent) HF hospitalization and all-cause mortality in all patients regardless of EF (COMPASS-HF, CHAMPION, REDUCE-HF and GUIDE-HF)



D+L = DerSimonian & Laird, EF = ejection fraction, HF = heart failure, HR = hazard ratio, IHM = implantable haemodynamic monitor, IRR = incidence rate ratio, I-V = inverse-variance

*Recurrent event effect estimates include HR for CHAMPION and IRRs for COMPASS-HF REDUCE-HF and GUIDE-HF.

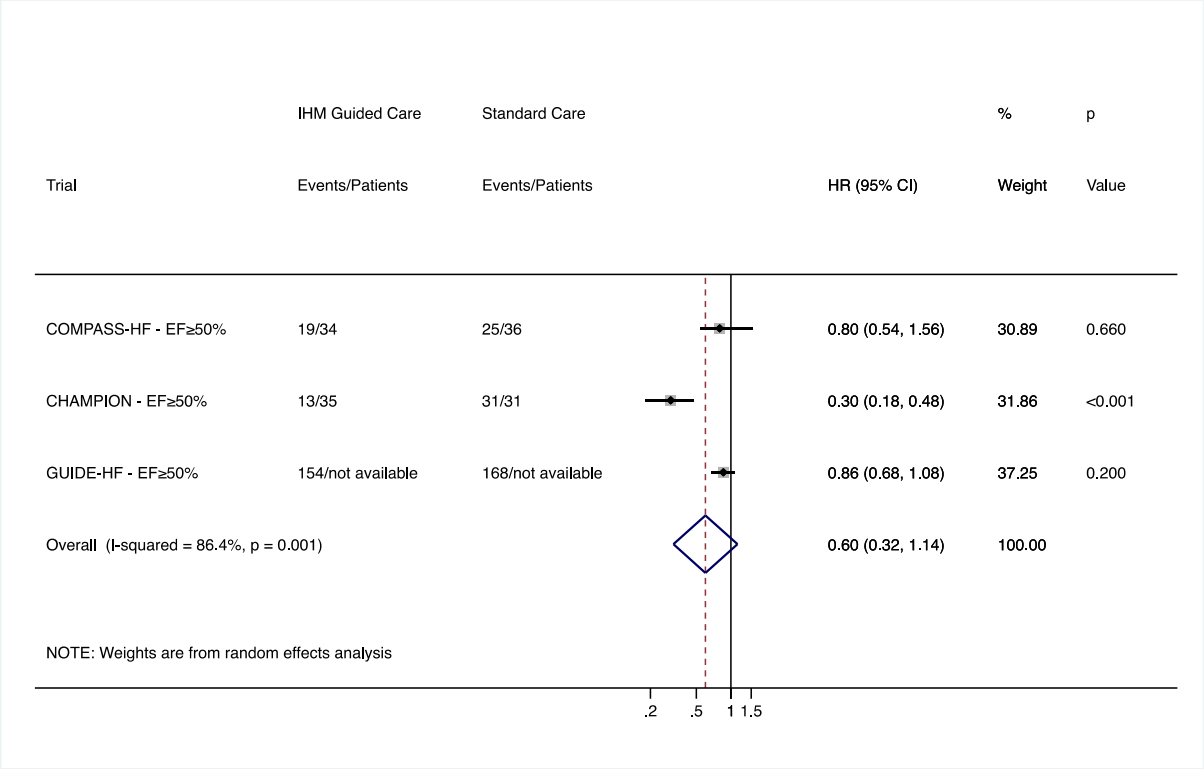
All-Cause Mortality and total worsening HF events: 680 events occurred in 1,103 patients in the IHM arm and 855 events in 1,121 standard care patients. IHM-guided care reduced all-cause mortality and worsening HF events by 20% [HR 0.81, 95% CI 0.69 – 0.94; moderate heterogeneity (I^2 49.9%)].

2.3.4 Patients with HFpEF (EF≥50%)

Data were available from COMPASS-HF and CHAMPION for 136 patients with an EF≥50%[46,268]. In the GUIDE-HF trial a HR and event numbers were reported but patient numbers for each randomised treatment group were not available[54].

Total worsening HF events: 186 events occurred in patients receiving IHM-guided treatment compared with 224 events in the standard care arm. IHM-guided care did not reduce worsening HF [HR 0.60, 95% CI 0.32 – 1.14; high heterogeneity (I^2 86.4%)] (**Figure 2-6**).

Figure 2-6 Total (first and recurrent) worsening HF events (HF hospitalization and ED and urgent clinic visit for IV HF therapy) in patients with HFpEF (EF>=50%)



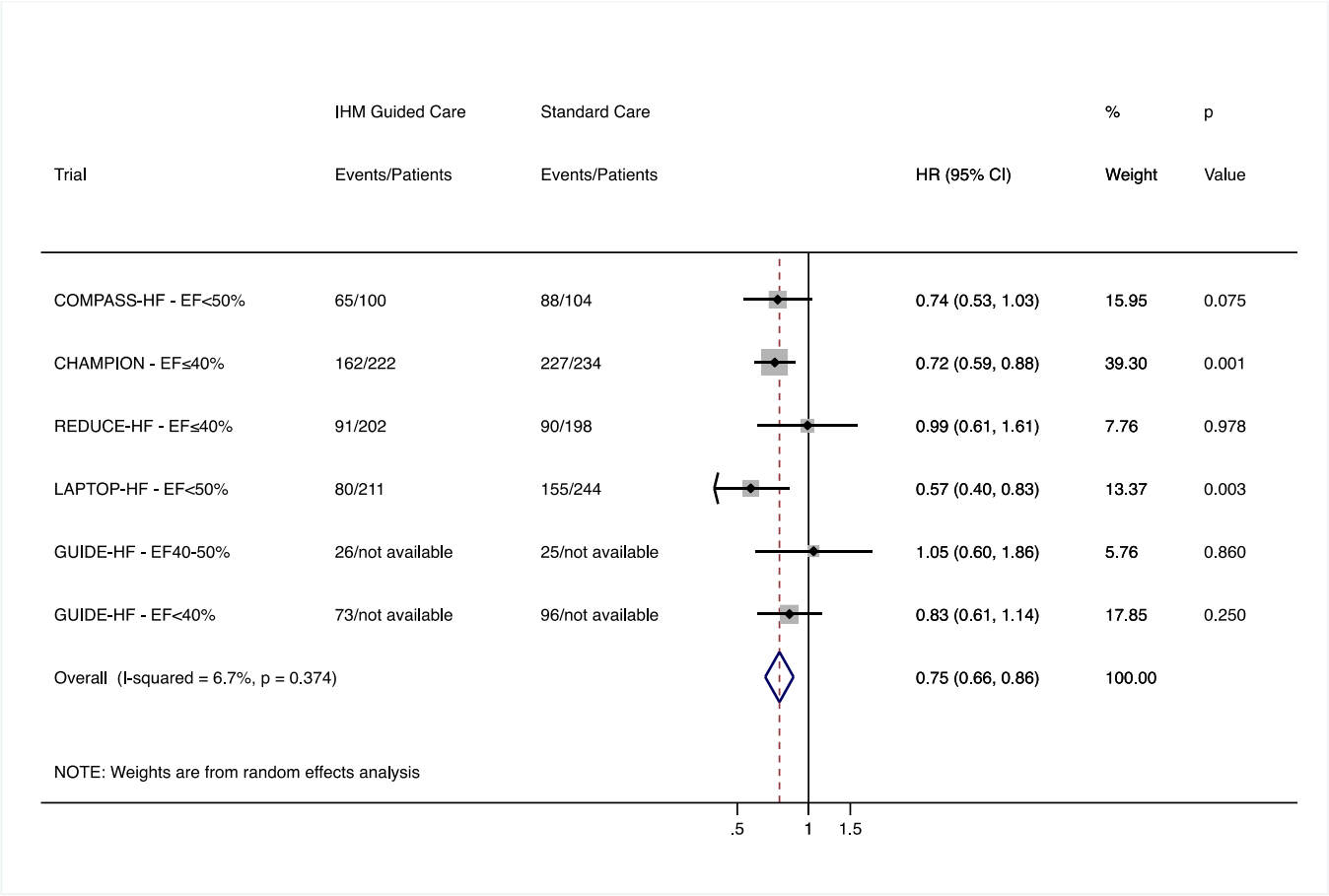
D+L = DerSimonian & Laird; ED = emergency department; EF = ejection fraction; HF = heart failure; HFpEF, heart failure with preserved ejection fraction; IHM = implantable haemodynamic monitor; IV = intravenous; HR = hazard ratio, IRR = incidence rate ratio
*Recurrent event effect estimates include HRs for GUIDE-HF and IRR for COMPASS-HF and CHAMPION.

2.3.5 Patients with HFrEF (EF<50%)

Data were available for 659 patients with an EF<50% from COMPASS-HF and LAPTOP-HF and for 856 patients with an EF≤40% from CHAMPION and REDUCE-HF. HRs and event numbers were reported for patients with an EF 40-50% and an EF<40% in GUIDE-HF but patient numbers were not available for each EF category in this trial.

Total worsening HF events: 497 events occurred in the IHM-guided care arm compared with 681 events in the standard care arm. IHM-guided care reduced worsening HF by 25% when compared with standard care [HR 0.75, 95% CI 0.66 – 0.86; low heterogeneity (I^2 6.7%)] (**Figure 2-7**).

Figure 2-7 Total (first and recurrent) worsening HF events (HF hospitalization and ED and urgent clinic visit for IV HF therapy) in patients with HFrEF (EF<50%)



D+L = DerSimonian & Laird, ED = emergency department, EF = ejection fraction, HF = heart failure, HFrEF = heart failure with reduced ejection fraction, HR = hazard ratio, IHM = implantable haemodynamic monitor, IRR = incidence rate ratio, IV = intravenous, I-V = inverse-variance
* Recurrent event effect estimates include HRs for CHAMPION, REDUCE-HF, GUIDE-HF and LAPTOP-HF and IRR for COMPASS

2.4 Discussion

The main results of this meta-analysis support the use of IHM in patients with symptomatic HF (irrespective of EF), demonstrating a 26% reduction in the risk of total worsening HF events, including hospital admission. This is the first meta-analysis to include total HF events from all IHM randomised trials, including LAPTOP-HF and the recently reported GUIDE-HF. I also report for the first time meta-analyses of the effectiveness of IHM-guided care in patients with HFrEF and HFpEF. The finding of a reduction in total worsening HF events in all patients regardless of EF was also present in patients with HFrEF, who comprised the majority of patients. The same benefit was not consistent in patients with HFpEF.

Patients with an EF<50% have been shown to have higher resting intra-cardiac and pulmonary pressures than those with HFpEF, and in turn, patients with higher pressures are at greater risk of decompensation from even small rises in pressure.[42,45,47] The relative reduction of total worsening HF events with IHM monitoring observed in this meta-analysis was comparable with the magnitude of benefit found in patients with HFrEF treated with an angiotensin receptor blocker-neprilysin inhibitor in the PARADIGM-HF trial (sacubitril/valsartan reduced HF hospitalizations by 21% compared with enalapril) and the sodium glucose co-transporter 2 inhibitor dapagliflozin in the DAPA-HF trial (dapagliflozin reduced HF hospitalizations by 30% compared with placebo)[269,270].

Mortality data were not reported from LAPTOP-HF and only 231 deaths were reported during the overall short average follow-up in the other four trials. With low numbers of deaths and limited follow-up periods no IHM trial demonstrated a reduction in mortality with IHM-guided care. Accordingly, the 22% reduction in the composite endpoint all-cause

mortality and HF hospitalization with IHM-guided care observed in this analysis was driven by the favourable effect on hospitalizations. The rate of HF hospitalizations calculated for the standard care arms in individual trials in this analysis ranged from 42 per 100 patient-years in REDUCE-HF to an estimated 147 per 100 patient-years in COMPASS-HF. The reported rate of total HF hospitalizations in the standard care arm of GUIDE-HF, which investigated the only currently available IHM (CardioMEMS) in the most contemporary HF population, was 49.7 per 100 patient-years[54]. This was markedly higher than the composite event rate for total HF hospitalizations *and* cardiovascular deaths in the placebo group of DAPA-HF (21.6 per 100 patient-years)[12]. The substantially higher hospitalization rates in the IHM trials highlight two considerations. First, that patients in these trials were highly selected and prognostically vulnerable. Second, rates of hospitalization will differ between the healthcare setting in which the IHM trials were conducted (USA predominantly) and that of other diverse settings of care as indicated by event rates in more international contemporary HF trials. The effectiveness, including cost-effectiveness, of such a targeted intervention as IHM and the system of care required to deliver it may accordingly differ depending on the setting and is an important consideration for future IHM studies.

To date, the main source of information on the effect of IHM in patients with HFpEF has been the CHAMPION trial. In that trial, the rate of HF hospitalization was 41 events per 100 patient-years in the IHM arm compared with 139 events per 100 patient-years in the standard care arm giving a 70% relative risk reduction in HF hospitalization among patients with an EF≥50% when treatment was guided by IHM.[46] Again, the rate of HF hospitalization was substantially higher in CHAMPION than observed in other contemporary trials of patients with HFpEF. In PARAGON-HF, the rate of HF hospitalization and cardiovascular death in the valsartan group was 14.6 per 100 patient-years.[271] The reliability of the relative

reduction for HF hospitalization in patients with HFpEF reported in the CHAMPION trial is limited by the small number of patients (n=66) included in that analysis. This new meta-analysis adds data on patients with HFpEF from COMPASS-HF and GUIDE-HF. With an additional 562 patients and 366 events, the fixed effect model demonstrated patients with HFpEF receiving IHM-guided treatment had a 28% relative reduction in total worsening HF events. In the random-effects model the average reduction was similar but the confidence intervals were wide, encompassing a potential 68% reduction to a 14% increase in such events with IHM-guided care. The difference in significance levels between models is in keeping with the high heterogeneity in the pooled sample. The effectiveness of IHM-guided treatment in patients with HFpEF remains uncertain and further trials are required with analyses in this population pre-specified in the study designs. On the available evidence, the patients who might benefit the most from IHM would have several characteristics, including a history of volume overload (as indicated by a recent HF hospitalization), persisting symptoms and an EF <50%.

2.5 Limitations

This analysis has limitations. Firstly, only two trials examined an IHM that is currently available (CardioMEMS) and three IHMs were examined over 18 years of investigation during which time the background management of patients with HF evolved with advancements in drug and device therapies.[269,270,272-274] Each IHM measured a different haemodynamic parameter. However, the IHM's haemodynamic measures were physiologically related [eg ePAD (COMPASS-HF) provided a surrogate estimate for left atrial pressure (LAPTOP-HF)]. Potential sources of bias exist. REDUCE-HF was terminated following concerns regarding four-year pressure sensor failure in patients from other Chronicle device studies. 400 patients from a recruitment target of 1,300 patients had enrolled at the point of study termination. Consequently, REDUCE-HF was under-powered, with only 181 events reported compared to the 648 events expected. LAPTOP-HF was also terminated early after one year due to peri-procedural safety concerns[263] and mortality data from this trial were not available. The meta-analysis effect estimates may have changed had both the REDUCE-HF and LAPTOP-HF trials achieved target recruitment. However, the inclusion of these studies in the meta-analysis reduced selection bias by including at least one-year of follow-up data on clinically relevant outcomes from these RCTs. Based on patients in REDUCE-HF and LAPTOP-HF having a mean EF of 23%±7 and 30%±15, respectively, both trials were included in the HFrEF analysis. The initial REDUCE-HF inclusion criteria also required participants to have an implantable cardioverter-defibrillator (ICD), favouring recruitment from a population with more severe HFrEF, the patient group in whom ICD implantation predominates. I cannot however completely exclude the possibility that some patients had EFs above these ranges. Individual cohort numbers were not available from all studies for all EF groups. I did not have

individual participant level data to test the interaction between ejection fraction and IHM-guided care.

The trials included in this meta-analysis all recruited selected patients who likely do not represent the broader population of patients with HF. These highly selected cohorts are typified by the people enrolled in the CHAMPION trial which had an inclusion criterion of patients in NYHA 3 functional class only, and the recruited cohorts had a mean age of 61 years. As stated above, none of these trials were double-blinded as investigators had access to which randomized arm the patients were enrolled into. Regardless of whether pre-written scripts were used to communicate with patients (in all trials bar LAPTOP-HF, patients were blinded), there is clear potential for bias to occur in the management of patients when healthcare providers had knowledge of their randomized status. The potential for bias in a single-blind trial design was highlighted in the CHAMPION trial when the Food and Drug Administration (FDA) in the United States investigated off-protocol communications between the device manufacturer and investigators who had access to patient randomization status.

2.6 Conclusions

IHM-guided treatment reduced total HF hospitalization and worsening HF events. In subgroup analyses, patients with HFrEF appear to benefit from IHM-guided care but whether the same benefit is present in patients with HFpEF remains uncertain. Further trials with pre-specified analyses of patients with an EF≥50% are required.

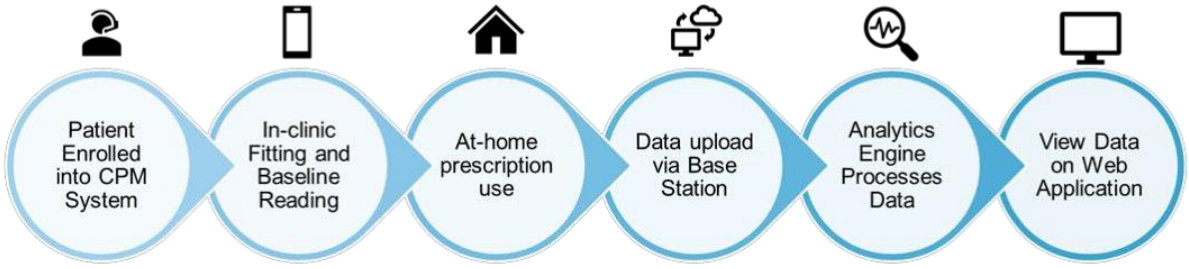
3. CHAPTER THREE. The CardioPulmonary Management (CPM) Device

3.1 The CardioPulmonary Management device

The CardioPulmonary Management (CPM) wearable device was developed and manufactured by Analog Devices Inc (ADI) (Wilmington, Massachusetts, USA). It was the investigational medical device (IMD) used in the CONGEST-HF clinical study. At the time of the study, the CPM device was a first generation, non-CE marked, class IIa medical device. The intended use of the CPM wearable device is for the remote-monitoring of patients with HF, to provide actionable information to clinicians, but not for the direct diagnosis of underlying cardiopulmonary disease.

The CPM device is intended to be part of a system of care, including patient self-management, whereby the device is applied by patients, their relatives or care-givers at home for 5 minutes twice-a-day (once in the morning and once at night). A CPM Mobile Application on the patient's mobile phone will be used to communicate with the wearable device and activate a reading. Data obtained from a device reading will then be sent to a Cloud from the device Base Station (a storage case and charging unit the device is housed in between readings). Cloud-based analytics will process the raw data into its derived measurements and the results will be provided to clinicians for review on a web-based platform (**Figure 3-1**). The images used in this section to describe the device were sourced from the manufacturer's instructions for use[275].

Figure 3-1 The intended use and structure of the CPM device system of care



3.2 CPM device components

The components of the CPM device are summarised in **Table 3-1**. Components marked with an asterix were not used in the CONGEST-HF study but are intended to be used within the system of care by patients at home.

Table 3-1 Components of the CPM wearable device

Component	Description	Used in CONGEST-HF
CPM wearable device	The measurement hardware used to collect study data at each visit	Yes
CPM device disposable adhesive	Patch, single-use adhesive and electrode hydrogels applied to the device electrodes and sensors to contact the patient's chest skin	Yes
CPM Analytics Engine	A numerical software package the computed physiological parameters and analysed physiological trends.	Yes

CPM Mobile App	An app installed on an Android mobile device to guide the user through the initial device reading setup and to monitor for quality of signals obtained throughout the reading.	Yes
Base Station Simulator	A software component used to (1) download the patient clinical data from the wearable device (2) apply a contemporary digital time stamp to the device prior to readings	Yes
Magnetic USB connector	An adaptor lead that connects by magnet to a port on the wearable device and by USB to (1) the study laptop to access the Base Station Simulator (2) a charging point adaptor	Yes
PC laptop	Base Station Simulator software was uploaded to the laptop	Yes
Base Station*	A cloud-connected gateway device used to charge the device and send information to a secure database	No – intended for home patient use
Cloud Platform*	Connected to the gateway Base Station device for receiving and storage of home-user physiological data.	No – intended for home patient use

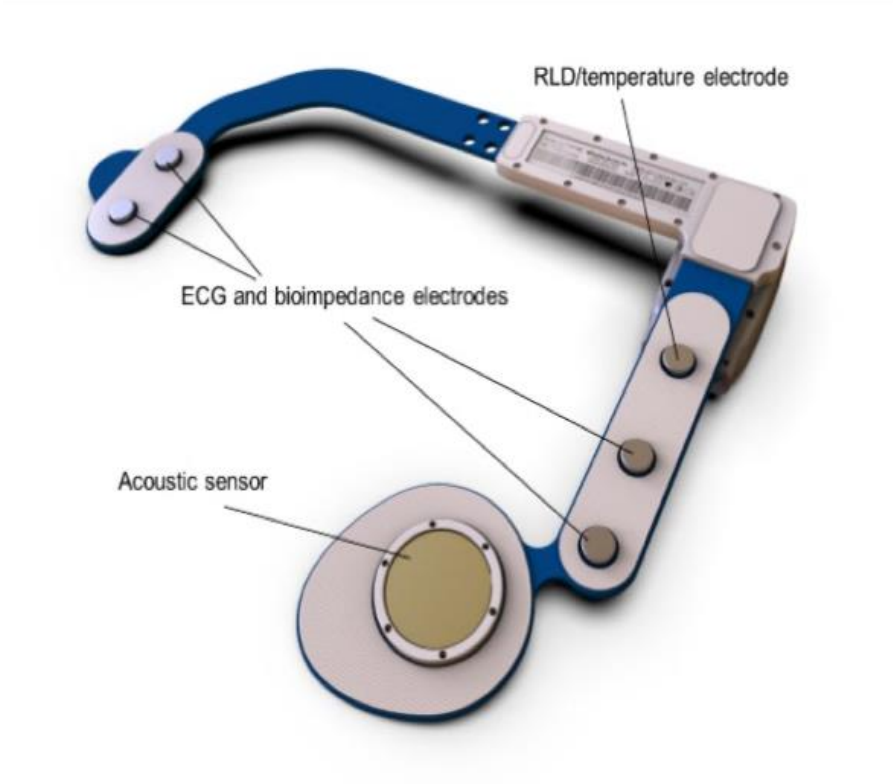
Web Services*	A website for healthcare professionals used to track patient trends	No – intended for home patient use
CPM Web Apps*	An app intended for use by medical professionals to manage the care of patients.	No – intended for home patient use

3.2.1 The CPM wearable device

The CPM device is a battery-operated, biocompatible wearable device manufactured from a rubber base material. It consists of one adhesive "island" just to the left of the sternum (left sternal border), one adhesive near the apex of the heart in the mid-clavicular line and another adhesive island under the left arm (near the middle axillary line) as shown in **Figure 3-2**.

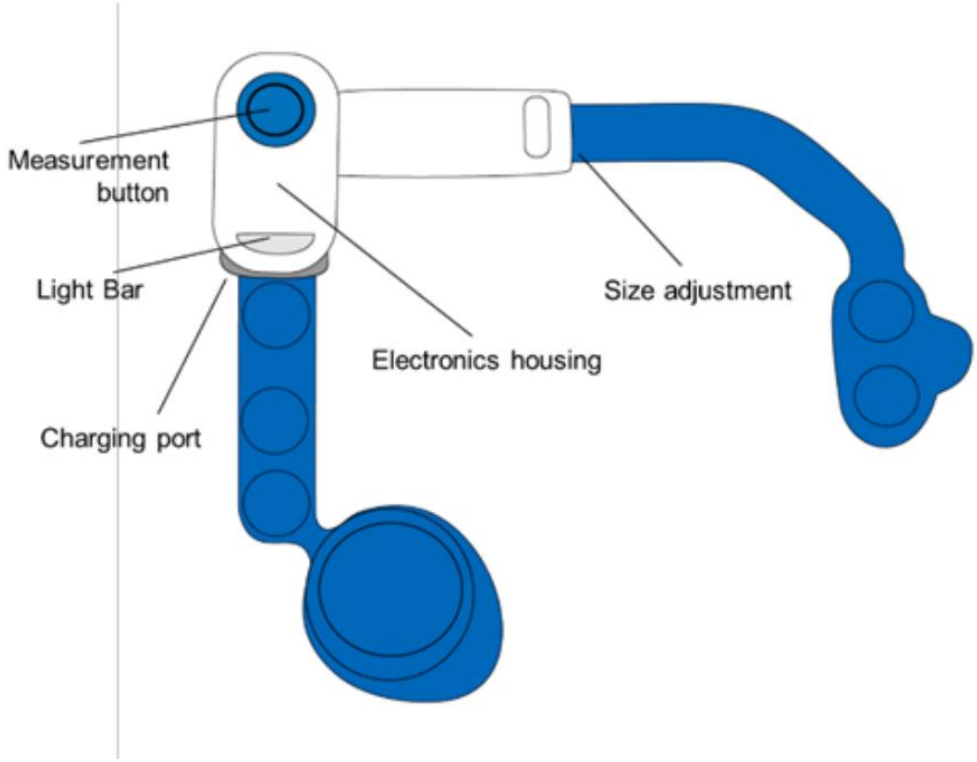
The measurement hardware contained in the device includes one round acoustic piezo sensor (electronic stethoscope) that is placed near the apex of the heart, five hydrogel electrodes [one of which is a right-leg drive (RLD) noise-reducing electrode while the other four collect ECG and bio-impedance signals], one temperature sensor and an accelerometer to measure tilt (body position).

Figure 3-2 The CPM wearable device sensor electrodes



The device features an adjustable mechanism to allow it to be sized to the patient and accommodate differences in chest circumference and breast size. An electronic housing unit is in the top medial section of the device. This unit contains the charging port which connects to a magnetic charging cable. A LED light bar indicates device status, including battery level and any device errors. A measurement button in the top part of the electronics housing unit is used to turn the device on/off (**Figure 3-3**).

Figure 3-3 CPM wearable device electronic components

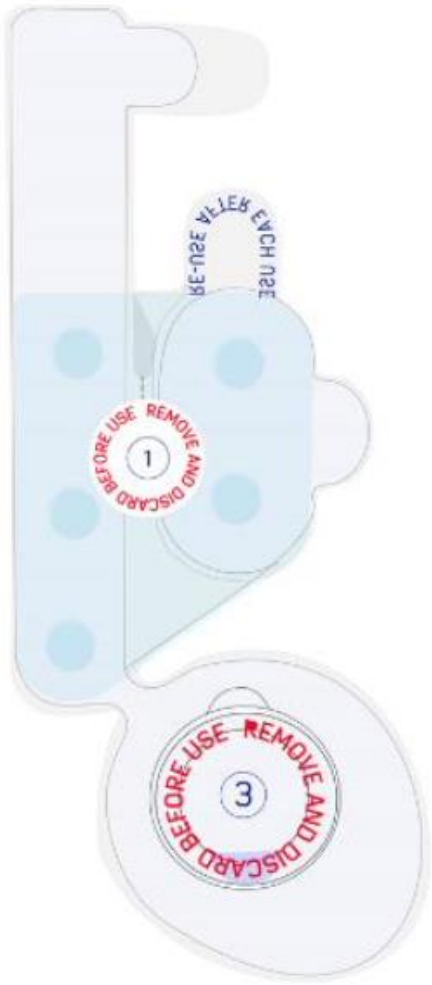


3.2.2 CPM wearable adhesives

During the CONGEST-HF study, the CPM wearable device was affixed to the patient's chest using disposable adhesive patches. The adhesive patches were single-use and changed for each study visit. Three peelable adhesive patch components consisted of a soft, velcro liner material and adhesive, pellet-like silicone hydrogels to contact the device electrodes; one adhesive part had three points of contact to cover the two ECG / bioimpedance electrodes and one to cover the RLD/temperature electrode on the major arm of CPM device. A second adhesive had two points of contact to cover the two ECG and bioimpedance electrodes on the minor arm of CPM device. The third part was the adhesive on top of the acoustic sensor. The hydrogel material is commonly used in ECG measurements and for acoustic piezo

sensor attachment to the skin. The adhesives provided a skin-electrode impedance to enable high quality bio-signal recordings.

Figure 3-4 CPM device disposable adhesives



3.2.3 CPM device Analytics Engine

The raw physiological data obtained by the device at the time of a study visit and stored on the wearable device was encrypted. As detailed below these raw data were then uploaded to a study laptop and transferred to ADI via the Robertson Centre for Biostatistics's secure

online SFTP portal. The ADI investigators used a tool called Offline Parser to decrypt the data and extract individual channels of physiological data. The decrypted data were further fed into an offline Analytics Engine (MATLAB algorithms, Natick, Massachucetts, USA) to extract the physiological parameters for every measurement. This CPM Analytics Engine derived measurements such as heart rate, respiration rate, relative tidal volume, thoracic impedance, body posture and diastolic heart sound energy from the raw measurement data acquired by the CPM device's sensors and electrodes. The derived measurements, along with trending information about these measurements, were generated and returned to the Robertson Centre for Biostatistics secure online SFTP portal. As detailed below, I was blind to the returning derived data. The offline Analytics Engine was functionally equivalent to the cloud-based Analytics Engine intended for use in the system when a patient is home monitoring.

3.2.4 CPM device Mobile Application

The CPM device mobile app was pre-loaded by ADI onto an Android mobile device supplied for use during the study. I used the mobile app to connect via Bluetooth with the CPM wearable device. The mobile app enabled me to pair each CPM wearable device ID to the participant's unique study ID in an individual match that ensured all device data obtained in a reading was recorded under the correct participant-device ID. Within the mobile app I viewed physiological parameter information as the device reading was being performed during a study visit. The mobile app provided signal information to confirm the device was operating properly, verified the placement of the device on the patient, and allowed me to

initiate and perform each measurement. Only I, as the clinical investigator, interfaced with the mobile app and patients were not allowed to access it.

3.2.5 CPM device Base Station Simulator (BSS) software

The BSS was a software tool that was provided by ADI and I installed onto a University of Glasgow study PC laptop. This software component enabled raw data obtained by and stored in the CPM wearable device to be downloaded onto the connected study laptop. In its intended use, a digital time-stamp of each reading will be recorded by the Base Station-Cloud interaction. However, because the Cloud was not part of the study, the BSS software provided a contemporary time-stamp for each study device reading (10 digits representing the number of seconds from 1970). Prior to each study visit, I connected the CPM device to the BSS software to ensure the time-stamp was updated.

3.3 Placement of the CPM wearable device

During the study, I placed the device on the chest of the participant as shown in **Figure 3-5**. Where necessary, male participants had chest hair shaved beforehand to ensure appropriate contact between the device's electrodes and the patient's skin. The CPM device was placed on the upper left chest area. The acoustic sensor was applied first, at approximately the 5^{th} intercostal space (standard for men) or 6^{th} intercostal space or the area just below where the breast attaches to the chest wall (for women). The device spans the left lung, with the larger side of the device (the side with the electronics housing unit, the "medial island") placed below the clavicular notch and just left of the sternum. The

smaller (“lateral”) island was placed vertically near the left mid-axillary line. The pairs of electrodes on the islands were aligned within the 3rd or 4th intercostal spaces. The central connecting bridge from sternal to lateral islands was kept horizontal and without tension. For each individual patient, the CPM device was placed repeatedly at the same anatomical landmarks for each study visit to ensure consistency across measurements. The electrodes and sensors were pressed down onto the chest skin to ensure good contact was achieved.

Figure 3-5 Schematic of the CPM device sensor locations on the left chest

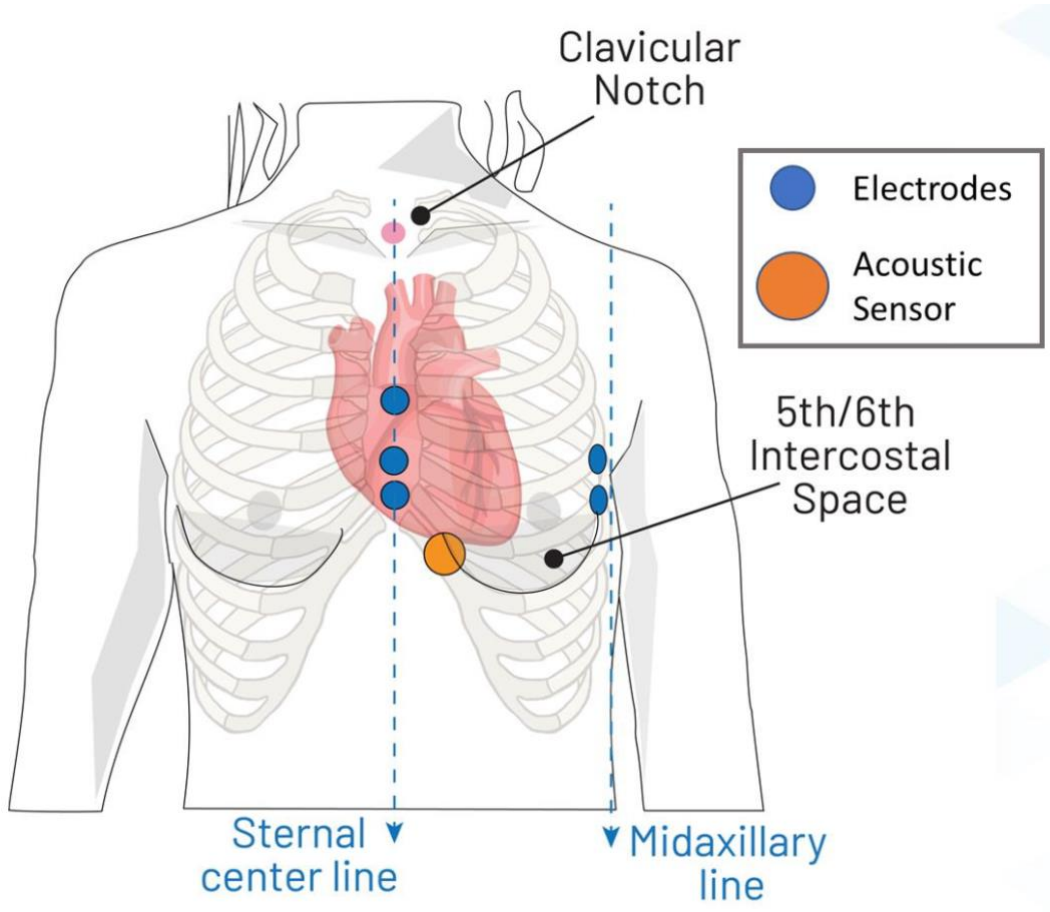
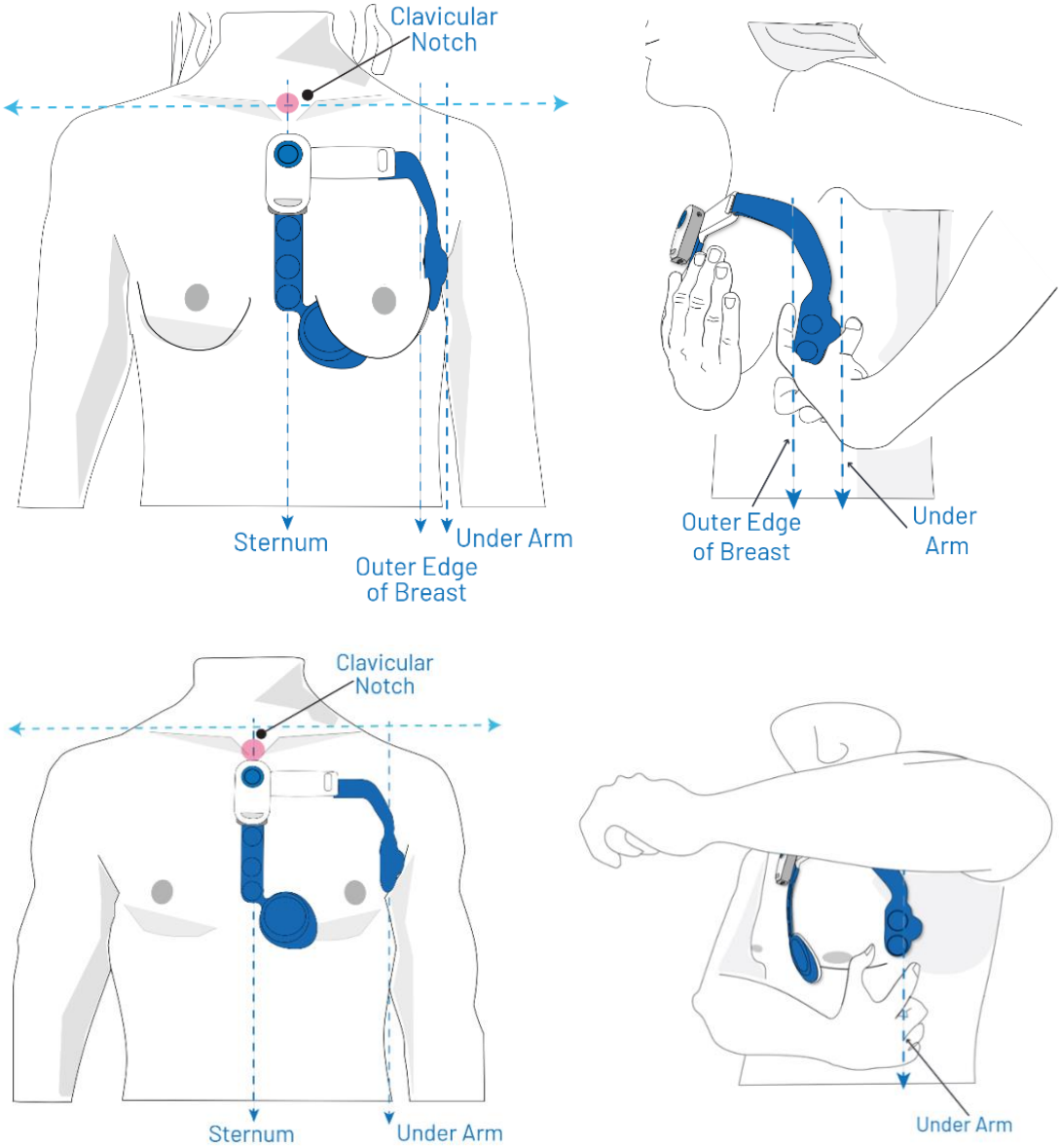


Figure 3-6 Schematic of the location of the investigational device on the left chest (left panel) on both female and male patients. Lateral view of the device placement (right panel).



3.4 Performing a CPM wearable device reading

In line with the pre-specified standard operating procedure and manufacturer's Instructions for Use (IFU), I took the following steps when performing a device reading:

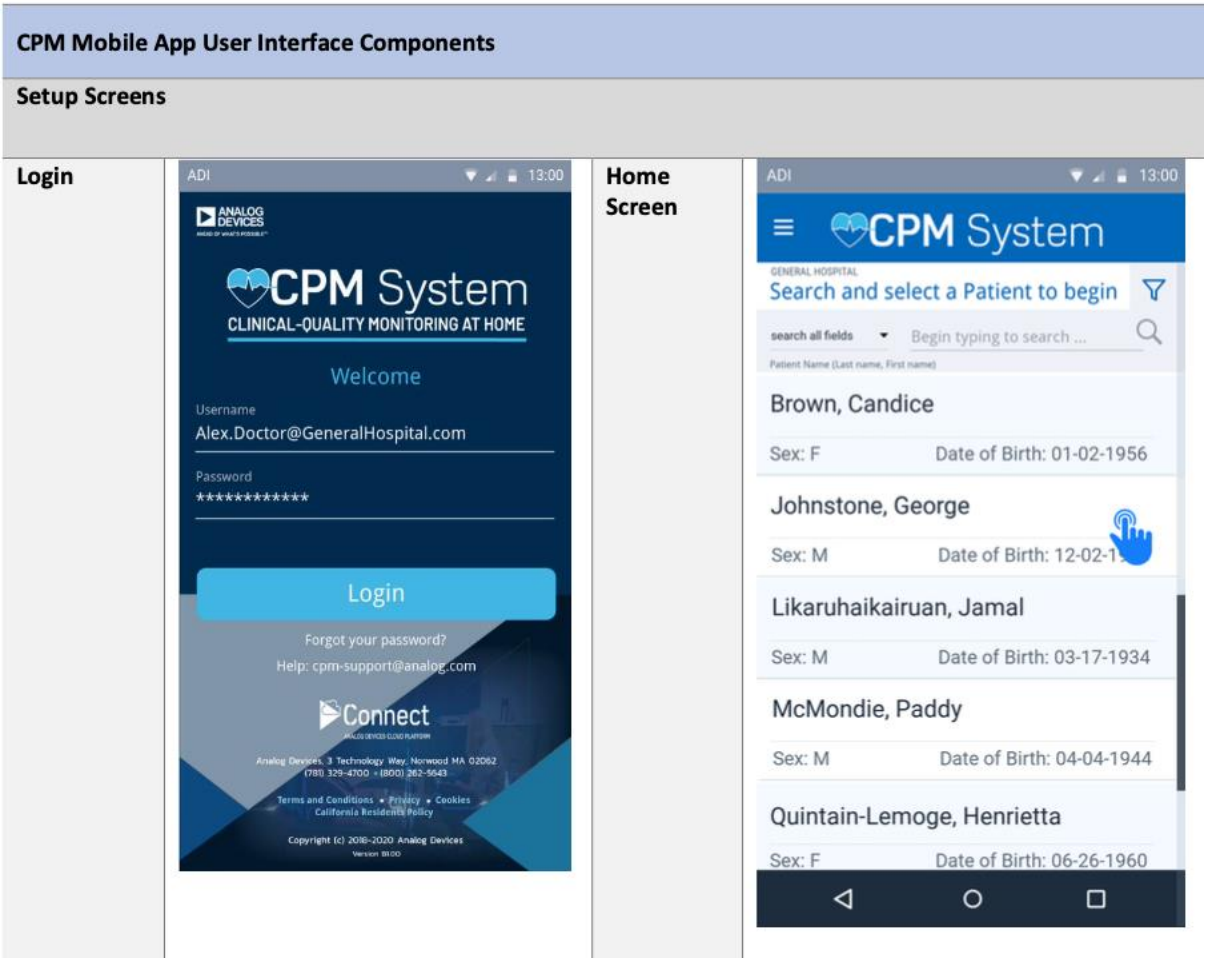
3.4.1 Device preparation and pairing to a participant

(1) I connected the CPM wearable device to the Base Station Simulator software and uploaded a contemporary digital time-stamp onto the device.

(2) I applied a new adhesive to the wearable.

(3) For the first use of a device by a participant, I logged into the CPM device mobile app and selected the participant's unique study ID which was pre-loaded by ADI onto the app.

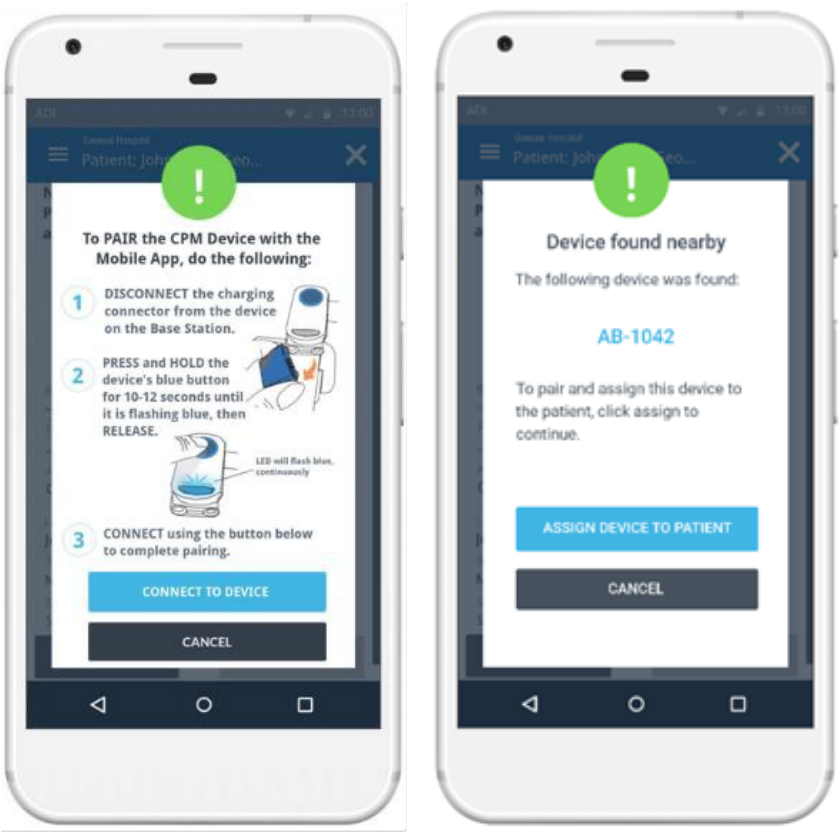
Figure 3-7 CPM device mobile app interface



(4) I pressed the Measurement button on the CPM device, which activated the Bluetooth Advertising Mode. This mode was identified when the LED began to flash blue (~10 seconds).

(5) I followed the app's prompts to "Connect to a device nearby".

Figure 3-8 Connecting the CPM device to the mobile app



(6) A popup window within the app listed any devices in range and I chose an appropriate, unassigned device from the list of Device Study IDs displayed using the "Assign Device to Patient" icon.

(7) A message "Device assigned and connected!" was then displayed on the screen and confirmed the unique pairing between study participant ID and device ID.

3.4.2 Taking a CPM device reading

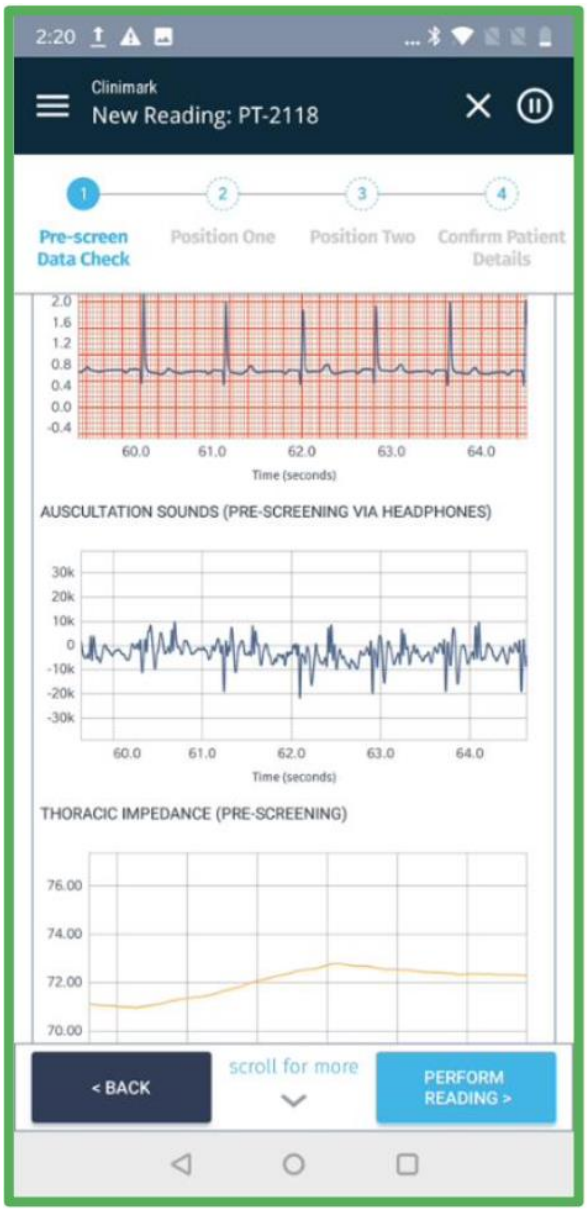
(1) I applied the CPM device to the patient as described above.

(2) The first measurement was performed with the patient sitting upright in bed (Position One).

(3) Within the CPM mobile app I selected the “Take Reading” and then “Start Reading” functions.

(4) The “pre-screen data check” then began and displayed ECG, auscultation and impedance signals to check if these were adequate.

Figure 3-9 CPM device ECG, diastolic heart sound energy and thoracic impedance signals



(5) With adequate signal quality confirmed, I selected the “Perform Reading” function on the app. This step determined the tilt that the patient had to achieve in Position

One for each subsequent measurement. The patient's back was supported (to avoid core muscle engagement being captured by the device) by elevating the rear of the hospital bed with the addition of pillows where necessary.

(6) The device performed "sweeps" for approximately 10 seconds. During this time, if there was an electrode contact error, the app indicated that the CPM device needed to be adjusted.

(7) The device then performed a measurement for 60 seconds, with visual data displayed on the app for quality control.

Figure 3-10 CPM mobile app screens to signal contact error, signal quality review during Reading 1 and an indicator page to prepare the patient for Reading 2

(8) On completing the first measurement sitting up, the patient was then placed in Position Two (as supine as they were able to tolerate). The second measurement of

the reading was then taken by repeating the same steps as for the first measurement.

(9) Two further readings were performed, for a total of three readings per study visit. Each individual reading consisted of a measurement in Position One and Position Two. Each reading lasted approximately 5 minutes.

(10) The CPM device was removed from the patient. The adhesive was discarded and the device cleaned with a medical, isopropyl alcohol wipe.

(11) I opened the Base Station Simulator software on the study laptop and connected the CPM device to it using the magnetic connecter lead. The raw data from the three readings was downloaded to the study laptop.

(12) I then accessed the Robertson Centre for Biostatistics's secure, online SFTP portal and uploaded the three raw data files into folders that were labelled using the participant study ID, device ID and visit number.

(13) These data files were then downloaded by the ADI study team and processed using the offline Analytics Engine into derived data. The derived study data were returned to the SFTP portal. I was blinded to the returned, derived data.

(14) The CPM device was then placed in its storage box and secure locker.

(15) I then completed the device tracking log (paper and electronic case report form).

As outlined in greater detail in Chapter 4, there were two main anticipated device-related adverse events. First was a potential interaction between the wearable and any pre-existing implanted devices (defibrillators or pacemakers). To prevent any untoward consequence from such an interaction occurring, during the wearable device readings I

monitored in real-time implanted device intra-cardiac electrocardiograms using a device programmer. No device-device interactions were observed during the CONGEST-HF study. The second anticipated adverse event was the development of an allergic skin reaction to the wearable device adhesive. Within 48 hours of every device reading I assessed the patients to determine if a reaction had occurred. If patients had been discharged and were not available for a face-to-face review, I phoned them within the same time frame. No adhesive related reactions occurred during the use of the study device. I recorded the details of all safety assessments in the electronic case report forms.

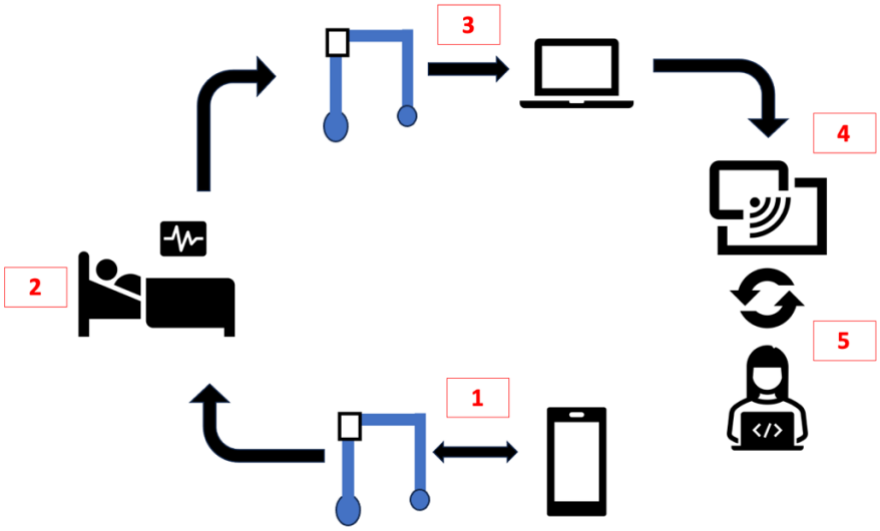
3.5 Flow of CPM device data during the study

The study objective was to examine the effectiveness of the CPM device to detect physiological measurements of clinical congestion. The feasibility of device use at home, including testing the wireless communication in a local environment was not under examination. Therefore, device components related to data communication to the Cloud or Cloud-based data processing were not part of the data management pathway in the study.

The sequence of data flow during the study is summarised graphically in **Figure 3-11** below. As previously described, the CPM mobile app and CPM wearable device were paired in a unique matching of participant and device study IDs over Bluetooth (1). The CPM device was then used to capture physiological data (2). The wearable was removed and raw physiological measurement data were downloaded onto the study laptop in an encrypted format (3). The three raw data reading files were uploaded to the secure SFTP Portal

managed by the Robertson Centre for Biostatistics (4). The Analog Devices Inc study team accessed the SFTP portal, decrypted and analysed the raw data into derived measurements using the offline Analytics Engine and returned the derived data files to the SFTP while I remained blinded (5).

Figure 3-11 CPM wearable device data flow, clockwise from bottom centre



3.6 CPM wearable device measurements

Raw device measurements are taken in either sweep and/or streaming modes. There was a sweep mode for approximately 10 seconds, followed by a streaming mode of 60 seconds followed by a final sweep mode for 10 seconds to obtain all of the measurements outlined below:

A. Temperature – obtained for 60 seconds in both Positions One (sitting upright) and Two (supine).

B. Impedance Spectroscopy – obtained for 10 seconds in both positions.

C. Streaming Impedance – obtained for 60 seconds in both positions.

D. Single Lead Electrocardiogram (ECG) – obtained for 60 seconds in both positions.

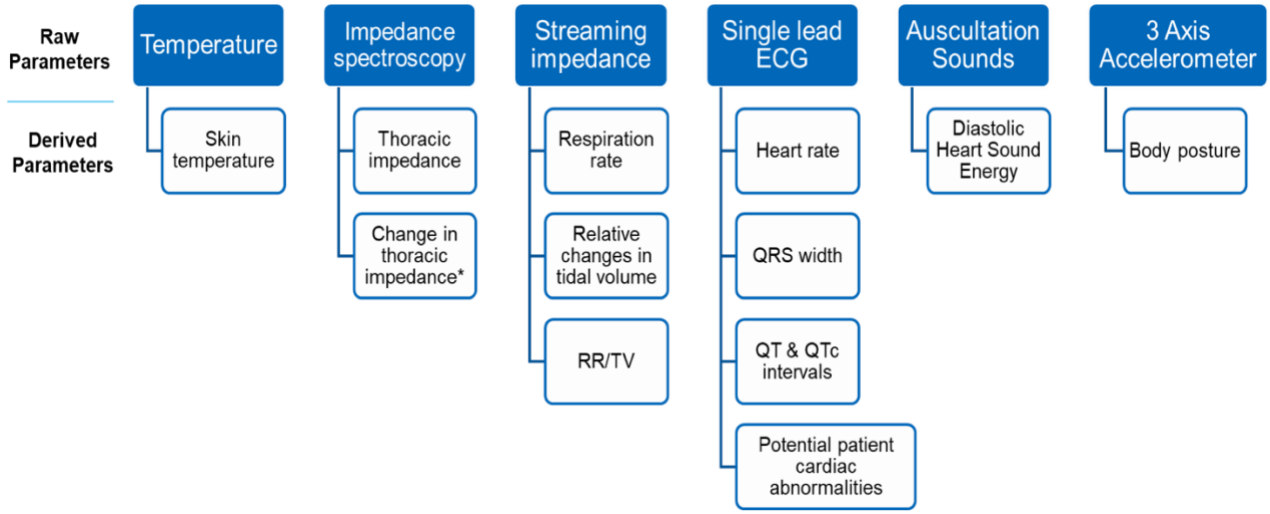
E. Heart Sounds – obtained for 60 seconds in both positions.

F. 3 Axis Accelerometer – data obtained continuously throughout the reading

The following derived measures were processed offline by the ADI study team from the raw data. The letter in parenthesis corresponds to raw measurement data above used to generate the derived measurement:

1. Skin temperature (A)
2. Thoracic impedance (B)
3. Change in Thoracic Impedance (B)
4. Respiration Rate (C)
5. Relative Tidal Volume (C)
6. Heart Rate (D)
7. QRS Width (D)
8. QT Interval (D)
9. Potential Patient Cardiac Rhythm Abnormalities (D)
10. Diastolic Heart Sound Energy (D/E)

Figure 3-12 Conversion of raw data into its derived physiological measurements.



3.7 Description of the Acquired and Derived Measurements

3.7.1 Skin Temperature

The CPM device collected temperature for 60 seconds in both position 1 and position 2. The average temperature during the last 5 seconds in each body position was determined and the higher average temperature (Position One vs Position Two) was reported as skin temperature.

3.7.2 Thoracic Impedance & Change in Thoracic Impedance

The CPM device collected impedance spectroscopy at a variety of frequencies in both body positions. The magnitude of thoracic impedance, at 100kHz excitation frequency, were computed from the information collected in both positions and displayed as the median impedance in each position (reported as “Thoracic Impedance 1 and 2”). Change in thoracic

impedance was a calculation of the difference in average thoracic impedance from one measurement position to the other (reported as “ΔZ”). Thoracic impedance and change in thoracic impedance were measured in ohms (Ω).

3.7.3 Respiration Rate (RR) and Tidal Volume (TV)

Streaming of impedance using 100 kHz excitation frequency was measured across the left side of the chest and streamed at a rate of 50 samples per second.

Following data quality and filtering, the Respiration Rate was derived using two methods: (i) time domain and (ii) autocorrelation. If the autocorrelation method reported high confidence of the presence of a dominant frequency component, then the respiration rate (RR) was reported based on autocorrelation; otherwise, RR was reported based on time-domain computation.

Tidal Volume (TV) measured by the CPM device was designed to perform as an analogue for the standard clinical tidal volume measurement. Tidal Volume was computed from the time domain method by computing the change in impedance [measured in ohms (Ω)] within one respiration cycle.

3.7.4 Respiration Rate/Tidal Volume (RR/TV)

RR/TV was an index computed from the ratio of respiration rate and relative tidal volume. An upward trend indicated an increase in respiration rate and/or a decrease in tidal volume, suggesting a rapid shallow breathing pattern in a patient with HF.

3.7.5 Heart Rate, QRS Width & QT Interval

The CPM device measured single lead ECG data. These data were processed to derive the Heart Rate, QRS width and QT Interval measures. Once data quality was confirmed and pre-processing of data was complete, the ECG R wave-peak was detected and heart rate was reported as a reciprocal of the median interval of the R wave-peaks. QRS width was calculated from the difference between the onset and offset of the QRS, which is determined based on a metric representing the QRS-like morphology. The reported value is the mean value from the lowest-angle posture. The QT interval was calculated from the difference between the onset of the QRS (Q wave) and the offset of T-wave. The offset of the T-wave was determined based on a metric representing T-wave like morphology. QTc was the corrected QT interval, accounting for the effects of heart rate and was calculated using the equation QTc = QT/$\sqrt{RR}$, where RR is the calculated R wave to R wave interval.

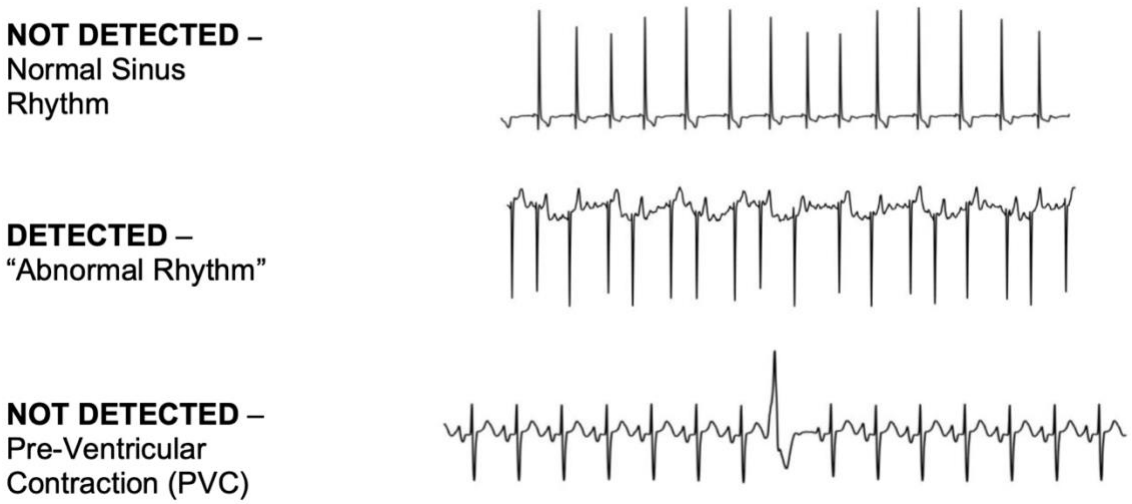
3.7.6 Potential Cardiac Rhythm Abnormalities

High-quality ECG tracings were processed to derive potential cardiac rhythm abnormalities algorithm based on the following computed metrics: (i) an entropy score to define how irregularly irregular the rhythm was and (ii) a score for the presence of a P-wave in each window. When developing the cardiac rhythm parameter, the parameter's algorithm weights were trained on a large publicly available PhysioNet repository (https://physionet.org/). The specific databases used from this repository were: MIT-BIH Arrhythmia Database, The MIT-BIH Atrial Fibrillation Database, MIT-BIH Normal Sinus Rhythm Database, MIT-BIH Supraventricular Arrhythmia Database and the Long Term AF

Database. After this training set, data collected from early versions of the CPM system were used to fine tune these parameters.

After training the algorithm, a weighted sum of the two scores was calculated. If the weighted sum crossed the limit (where irregular rhythm and absence of P-wave result in a higher metric), the ECG tracing was declared to be “potentially abnormal”. This measure was not diagnostic of AF which needs to be confirmed clinically (eg by 12 lead ECG) but is intended to provide an alert to clinicians that a patient is at risk of AF and may provide information on a potential cause of decompensation. Examples of rhythm discrimination are detailed in **Figure 3-13**.

Figure 3-13 Binary identification of potential cardiac rhythm abnormality by the CPM device rhythm algorithm with the absence of P waves and an irregularly-irregular rhythm



3.7.7 Third Heart Sound Energy (S3)

The detected QRS complex from the ECG signal was used to define the start of systole. The heart sound auscultation data was then used to detect the first (S1) and second (S2) heart sounds by detecting energy peaks in the auscultation signal (moving root mean square in a 30ms window). Then an offset was applied to the S2 location and was defined as the start of diastole. The end of diastole was defined as the interval before the next QRS complex. The moving energy (average square) was computed between the start and end of diastole over a moving window of 85 milliseconds width. The heart sound energy in diastole (S3) measurement was defined as the maximum of this moving average defined in the previous point. S3 energy was measured using a proprietary, arbitrary unit (AU).

3.8 Handling Conditions

In line with the manufacturer's instructions, all components of the CPM device were handled and stored at a temperature between -10°C and 45°C.

3.9 Shelf life

The CPM wearables were assigned a 6-month shelf life and a 1-year operating life (18 months in total). Adhesive pads were assigned an overall lifetime of 6 months (to include shelf life and use) with a use-by date on each packet.

3.10 Study device storage and supply

Investigational medical device supplies were only released to the study site by ADI once all the appropriate regulatory and governance approvals were in place. Devices and adhesives

were delivered to the clinical research facility at the Queen Elizabeth University Hospital (QEUH), Glasgow care of my attention. I transferred the devices to the Golden Jubilee National Hospital (GJNH), Glasgow for Cohort A, with the remaining devices remaining on site in the QEUH for Cohorts B and C.

All study devices were stored in a designated locked, secure cupboard with access limited to the study team and authorised site staff. Study supplies were not used on any persons other than study participants. The device manufacturers returned devices to me for use by other, future participants. Devices that were returned to me by ADI had been cleaned and any previously acquired data deleted. A new device ID was assigned to any device returning to me so that a new unique match could be made between the new participant's ID and the returned device ID.

Throughout the study, I monitored the stock of devices and adhesives and made orders from ADI for further supplies as required. I returned used devices to the manufacturers using a designated study account with Eagle Couriers.

3.11 Device Traceability

Study devices were labelled with a serial number and assigned to one patient only. Device serial numbers were recorded on the electronic CRF so devices could be matched to patients within the dataset. I recorded the location of each device throughout the study on paper and in the electronic CRF.

4. CHAPTER FOUR. Design and methods of the Correlation of the non-invasive Cardiopulmonary Management (CPM) system with measures of congestion in heart failure (CONGEST-HF) study

4.1 Introduction

As described in the Introduction section, hospitalization for HF represents a major burden to health services and is associated with poor clinical outcomes including mortality. The majority of hospitalizations for HF are due to the fluid retention leading to volume overload which is a hallmark of the HF syndrome. The use of diuretics to relieve congestion and maintain euvolaemia is considered by many as being synonymous with a diagnosis of HF. The ability to pre-empt clinical decompensation by detecting physiological changes consistent with the emerging development of congestion is highly desirable so that patients could be assessed and treatments targeted at averting a costly admission could be initiated.

Analog Devices Inc developed the wearable patch-like Cardio-Pulmonary Management (CPM) device to assess congestion levels by measuring a number of physiological parameters over approximately five minutes. The CPM wearable device had not been previously studied in patients who were actively experiencing changes in congestion status following treatment. Therefore, I designed the Correlation of the non-invasive Cardiopulmonary Management wearable device with measures of congestion in heart failure (CONGEST- HF) study to determine if the CPM device could accurately detect the presence of congestion by correlating

the findings of the device parameters with the findings of gold standard assessments of congestion used in the clinical management of patients with congestion.

4.2 Study Design

CONGEST-HF was a prospective observational study, designed to examine if the measures derived from the CPM wearable device correlated with measures of congestion in patients who were at risk of or actively experiencing congestion.

4.2.1 Blinding

As described in the previous Chapter, I and the patient's usual medical team were blind to the data collected by the CPM wearable device. Device data were downloaded, stored on the RCB secure SFTP server and accessed by ADI for processing. Derived data were then returned to the SFTP portal. I did not have access to the returned, derived data files. ADI did not have access to any other study data collected (eg patient details, blood tests, ultrasound findings). Blinding was maintained until the database was locked at the end of the study.

4.2.2 Patient Co-design

To ensure patients' viewpoints and input were incorporated into the study design I presented the study to five inpatients on the Cardiology wards at the QEUH. These were people representative of the patients in Cohort C. I gave them the Patient Information Sheet (PIS) and consent form to read and discussed the study with them. Verbal and written (by anonymous questionnaire) feedback was received on the study plan and information leaflet. Four of the five patients said they would have taken part in the study. The only patient who said they would have declined did so because they did not see any immediate benefit to them in taking

part. No patient voiced any concerns about a risk to patient welfare due to the study design. I conducted this interaction with patients prior to submission for ethical and regulatory approval.

4.2.3 Ethical approval

Prior to enrolment of the first patient, ethical approval to conduct the study was sought and received from the London-Dulwich Research Ethics Committee (REC): REC Reference Number: 21/LO/0465. The study was be carried out in accordance with the World Medical Association Declaration of Helsinki (1964) and its revisions (Tokyo [1975], Venice [1983], Hong Kong [1989], South Africa [1996] Edinburgh [2000], Seoul [2008] and Fortaleza [2013]).

4.2.4 Medicines and Healthcare products Regulatory Agency (MHRA) approval

MHRA approval to conduct the study was sought and received prior study commencement. The application process was a detailed, shared endeavour. The University of Glasgow (UOG) study team (Prof Pardeep S Jhund, Dr James P Curtain, Dr Katriona Brooksbank, Ms Joanne O'Donnell) provided clinical and study design expertise, the ADI team provided the necessary and extensive manufacturer's information, a representative from the study Sponsor [NHS Greater Glasgow & Clyde (NHS GGC)] provided application oversight, and an external party Quality, Regulatory and Clinical Consultancy (QRCC) were engaged by the UOG team to act as the Sponsor's representative for the application and provided guidance on the application process.

4.2.5 Study Sponsorship

The study was sponsored by NHS GG&C Research and Innovations. Sponsor responsibilities undertaken by NHS GG&C were as defined in the Research Governance Framework for Health and Community Care (Second edition, February 2006).

4.2.6 Study Funding

The study was funded by an investigator-initiated grant provided by the device manufacturer ADI, including the supply of the devices. Given the novel technology and requirement to transfer encrypted, de-identified data to the manufacturer, it was necessary to collaborate with ADI on aspects of the study design. The device manufacturer did not have access to participant identifiable information, collected study data (other than the wearable device data), or have final opinion on the study design or the decision to submit the results for publication.

4.2.7 Statement of Indemnity

NHS indemnity was provided under the Clinical Negligence and Other Risks Indemnity Scheme (CNORIS). The UOG provided indemnity for harm arising from the design of the study. ADI were liable for harm caused by the CPM wearable device.

4.3 Study hypothesis

Fluid status and congestion can be determined by the CPM wearable device and correlates with invasive measures, non-invasive measures and biochemical markers of congestion and changes in congestion.

4.3.1 Primary objectives

In Cohort A, the primary objective was to investigate if measures derived by the CPM device correlated with invasive measures of cardiopulmonary haemodynamics.

In Cohort B, the primary objective was to investigate if measures derived by the CPM device and changes in these measures correlated with B-lines on LUS and changes in B-lines before and after haemodialysis and with volume of fluid removed during haemodialysis.

In Cohort C, the primary objective was to investigate if measures derived by the CPM device and changes in these measures correlated with B-lines on LUS and weight during treatment for HF.

4.3.2 Secondary objectives

Cohort A, B, C: To determine the correlation between tidal volume measured by the CPM wearable device and tidal volume measured with spirometry.

Cohort A: To determine the correlation between congestion measured by the CPM wearable device and physical symptoms and signs, further RHC measures, LUS and transthoracic echocardiography.

Cohort B: To determine the correlation between congestion and change in congestion measured by the CPM wearable device and clinical measures of congestion (physical symptoms and signs and echocardiography findings).

Cohort C: To determine the correlation between congestion and change in congestion measured by the CPM wearable device and clinical measures of congestion (physical symptoms and signs and echocardiography findings).

4.3.3 Exploratory objectives

Cohorts A, B and C: To determine the correlation between congestion and change in congestion measured by CPM wearable device and the value and change in value of NT-ProBNP, MR-proANP and blood haematocrit.

Cohorts A, B and C: To determine the correlation between congestion and change in congestion measured by the CPM wearable device and the percentage and change in percentage of LV GLS on echocardiography.

Cohorts A, B and C: To determine the correlation between CPM device-measured heart rate and clinical examination heart rate, and the relation between the CPM device assessed heart rhythm parameter and the presence of an irregular heart rhythm on clinical examination.

4.3.4 Endpoints

As this was an observational study there were no clinical endpoints.

4.4 Patient Population

Male and female patients aged ≥18 years with a primary diagnosis of HF (Training cohort, Cohort A and Cohort C) and inpatients on chronic haemodialysis (Cohort B) were recruited CONGEST-HF. The inclusion and exclusion criteria for each cohort are detailed below.

4.4.1 Training Cohort

Prior to commencing recruitment for the CONGEST-HF study, I enrolled 5 participants as a training cohort to allow me to practice applying the device, performing the device readings and uploading the raw, non-identifiable data onto the RCB's secure SFTP platform. I used this cohort to verify the process of blinded data transfer, whereby ADI downloaded the training cohort's raw data, processed it into derived device data and subsequently returned this derived data to the RCB. The training cohort were inpatients at the QEUH with the same inclusion criteria as Cohort C. One training visit only per patient was conducted. The training cohort were assigned unique identifier numbers similarly to the main study cohorts and were recorded in the eCRF. Apart from a medical history and physical exam (required to apply the device), no other study assessments were performed (eg no ultrasound imaging or biomarkers). Participants in the training cohort received the same adverse event surveillance as participants in the main study. Participation in the training cohort did not influence the standard medical care the patients received. Data obtained from the training cohort were not included in the final study analysis.

4.4.2 Cohort A

Patients in Cohort A were recruited on the Scottish National Advanced Heart Failure Unit at the GJNH. This cohort consisted of both inpatients and patients who were having a planned RHC as part of advanced HF management. Study data, including the CPM wearable device readings, were gathered prior to the RHC. All decisions regarding the clinical management of the patient were made by the clinical care team with no knowledge of any of the measurements obtained from the CPM wearable device or any of the other study procedures apart from the RHC.

4.4.3 Cohort B

Patients in Cohort B were recruited from Ward 4D at the QEUH. Cohort B had a diagnosis of chronic renal failure and were established on haemodialysis for ≥90 days. Study data were gathered before and after a single haemodialysis session. All decisions regarding the clinical management of the patient were made by the clinical care team with no knowledge of any of the measurements obtained from the CPM wearable device or any other study procedure.

4.4.4 Cohort C

Patients in Cohort C were recruited from the cardiology wards or acute receiving unit (ARU) at the QEUH if they were admitted for decompensated HF and were receiving IV diuretic therapy. Data were gathered on the day of enrolment, the day after enrolment, the day the patient transitioned from IV to oral diuretics (day of first dose of oral diuretic) and the day of discharge. All decisions regarding the treatment of the patient, including switching from IV to oral diuretics and when the patient was discharged were made by the clinical care team with no knowledge of any of the measurements obtained from the CPM wearable device or any of the other study procedures.

Patients were required to satisfy all of the eligibility following criteria. Eligibility waivers to the inclusion / exclusion criteria were not permitted.

4.4.5 Inclusion Criteria

- Written informed consent
- Male or female ≥18 years of age
- Training Cohort
    - ESC criteria for diagnosis of HF[2], including heart failure with reduced (HFrEF), mildy reduced (HFmrEF) and preserved (HFpEF) ejection fraction.
    - Requiring treatment with IV diuretics
- Cohort A
    - ESC criteria for diagnosis of HF[2], including heart failure with reduced (HFrEF), mildy reduced (HFmrEF) and preserved (HFpEF) ejection fraction.
    - Undergoing clinically-indicated right heart catheterisation (RHC)
- Cohort B
    - Established on haemodialysis for >90 days.
    - Undergoing haemodialysis with a target volume removal ≥1.5 litres fluid
- Cohort C
    - ESC criteria for diagnosis of HF[2], including heart failure with reduced (HFrEF), mildy reduced (HFmrEF) and preserved (HFpEF) ejection fraction.
    - Requiring treatment with IV diuretics

4.4.6 Exclusion Criteria

- Unable to consent to inclusion in study due to cognitive impairment
- Pregnancy or breastfeeding
- Any skin condition preventing attachment of the device to the patient
- Any chest wall or breast abnormality that would prevent the accurate attachment of the device to the patient
- Any allergy to silicon-based adhesives
- Any other allergy to medical dressings
- Uncontrolled cardiac arrhythmia
- Conditions that may confound congestion assessments, including
    - severe obstructive lung disease- Gold Stage >3
    - fibrotic lung disease- extensive lobar involvement on chest CT in territory of LUS zones
    - severe liver disease- Childs Pugh C
    - relevant active malignancy, including lung cancer, pelvic cancer with caval compression, superior vena cava obstruction syndrome
    - active bronchopneumonia- chest X-ray within 4 weeks showing consolidation
    - pneumonectomy or lobectomy
    - pulmonary embolism within the previous 3 months
    - Cohort A only: haemodynamically significant mitral stenosis (at least moderate in severity on echocardiography)
    - active pneumothorax
    - pulmonary contusion
    - indwelling intercostal chest drain

- active implanted LVAD
- COVID-19 infection

4.4.7 Women of child-bearing potential

Women of child-bearing potential were eligible for enrolment in the study. A negative pregnancy test result was required.

4.4.8 Co-enrolment in other studies

As this was an observational study with no influence on clinical management, enrolment in other studies was permitted as long as it was considered that co-enrolment did not represent an excessive burden to the patient.

4.4.9 Screening and identification of participants

All patients without obvious contraindications to enrolment based on a review of case-notes were approached with regards to taking part in the training cohort or in the main study. Patients were identified by the primary care teams as being potentially eligible for recruitment. I explained the study, including a demonstration with the device. Participants were provided with a cohort-specific patient information sheet (PIS) and given the opportunity to ask questions. A sample PIS is included in the **Appendix**. All patients who were screened were recorded in paper format in the study screening log which was kept securely in the site file.

4.4.10 Consent

Assenting patients who met the eligibility criteria and without any contraindications to taking part in the study had their written, informed consent documented according to Good Clinical Practice (GCP) and the International Organization for Standardization guidelines for clinical investigation of medical devices for human subjects (ISO 14155:2020). A sample consent form is included in **Appendix.** Enrolled patients were allocated a unique patient identifier number that lasted for the duration of the study. I assessed the eligibility and obtained informed consent process for every patient in the study, having extensive experience throughout my Cardiology training in taking informed consent. Patients were given a minimum of 12 hours from initial approach to consent to consider taking part in the study.

A photocopy of the consent form was given to the participant and another was uploaded to the participant's eCRF. The original consent form was filed in the study site file and a copy was kept in the participant's clinical notes. All patients who were recruited were recorded in paper format in the study recruitment log, kept securely in the site file, along with their unique study ID.

4.5 Study schedule and assessments

Participants in the training cohort were assessed on one visit during their admission to receive HF treatment at the QEUH. The study visits by the other cohorts are outlined in the flow charts below. Cohort A were assessed on the day of RHC so that the device measures could be correlated most robustly with invasive haemodynamics, whether these people were heavily congested inpatients or elective cases. The study design allowed for participants to be assessed serially if repeat RHCs were performed. As the RHCs were performed as part of

standard care, many congested patients were escalated to higher forms of circulatory support such as intra-aortic balloon pumps or left ventricular assist device which ended further potential study participation regardless of whether a repeat RHC was performed. This diminished the potential for change in PCWP to be correlated with change in device measures. In cohort B, the device was correlated with clinical measures of congestion immediately before and after volume was removed, so that the sensitivity of the device to detect rapid, clinically relevant shifts in fluid could be examined. In cohort C, the four pre-specified study intervals were chosen for their expected clinical relevance. Visit 1 in cohort C was a baseline visit, when patients were expected to be most volume overloaded. Typically, patients lose the greatest proportion of volume within the first 48 hours of treatment, particularly if diuretic naïve. The research ethics committee required participants to be given a minimum of 12 hours before consent could be obtained, in which time diuresis was taking part and potentially uncaptured changes in congestion markers were occurring. As detailed in Chapter 7, patients in cohort C were heavily congested on enrolment. Study visit 2 was intended to capture the first rapid, anticipated change in volume status. Visit 3 and visit 4 represented important clinical stages that clinicians would identify as markers of stability and the achievement of euvolaemia when patients are successfully established on oral therapy. These final two visits also allowed for the greatest anticipated points of decongestion to be evaluated and examine whether the device was only sensitive to large or more subtle shifts towards euvolaemia.

Figure 4-1 Cohort A Study Flow Chart

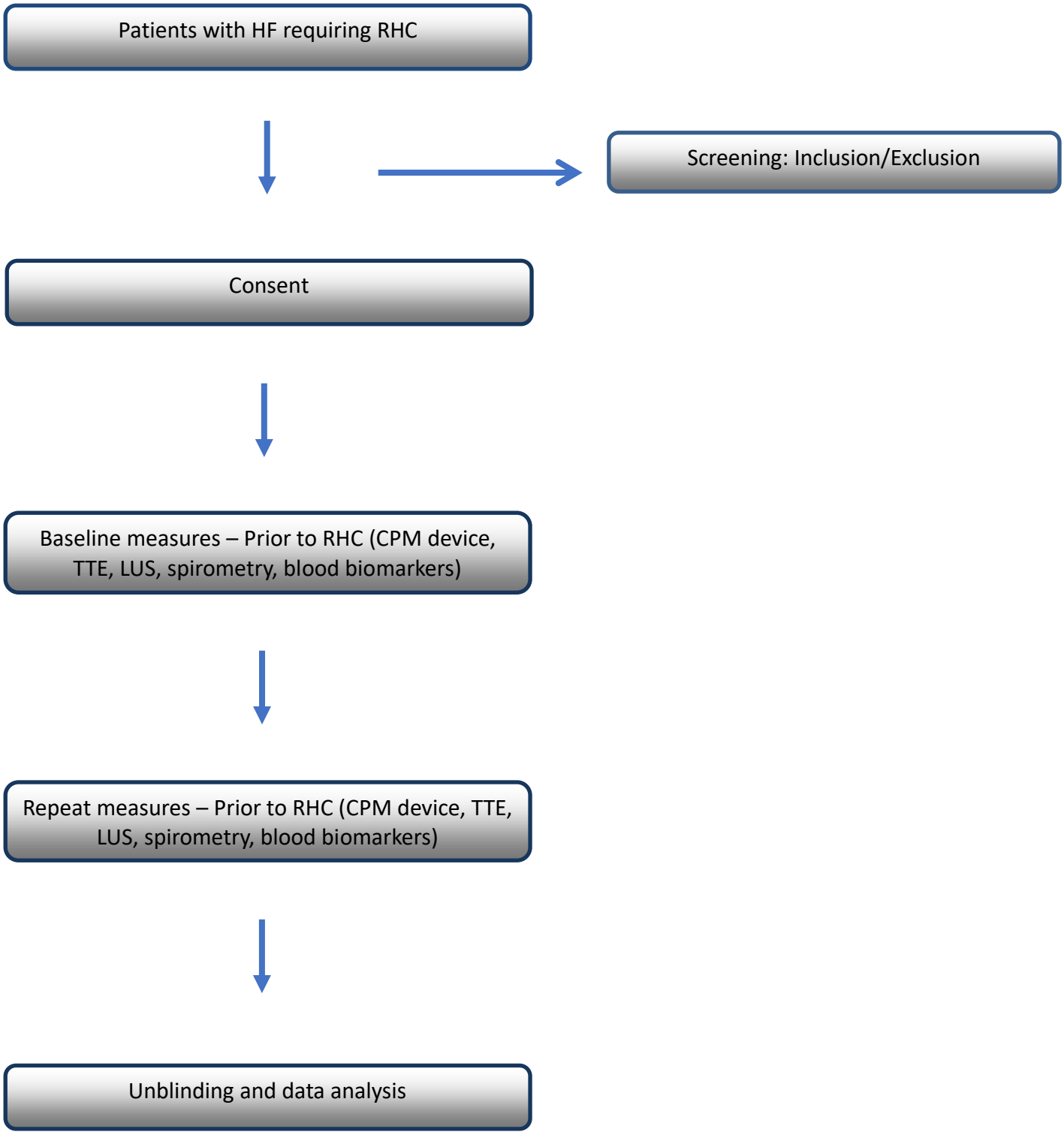


Figure 4-2 Cohort B Study Flow Chart

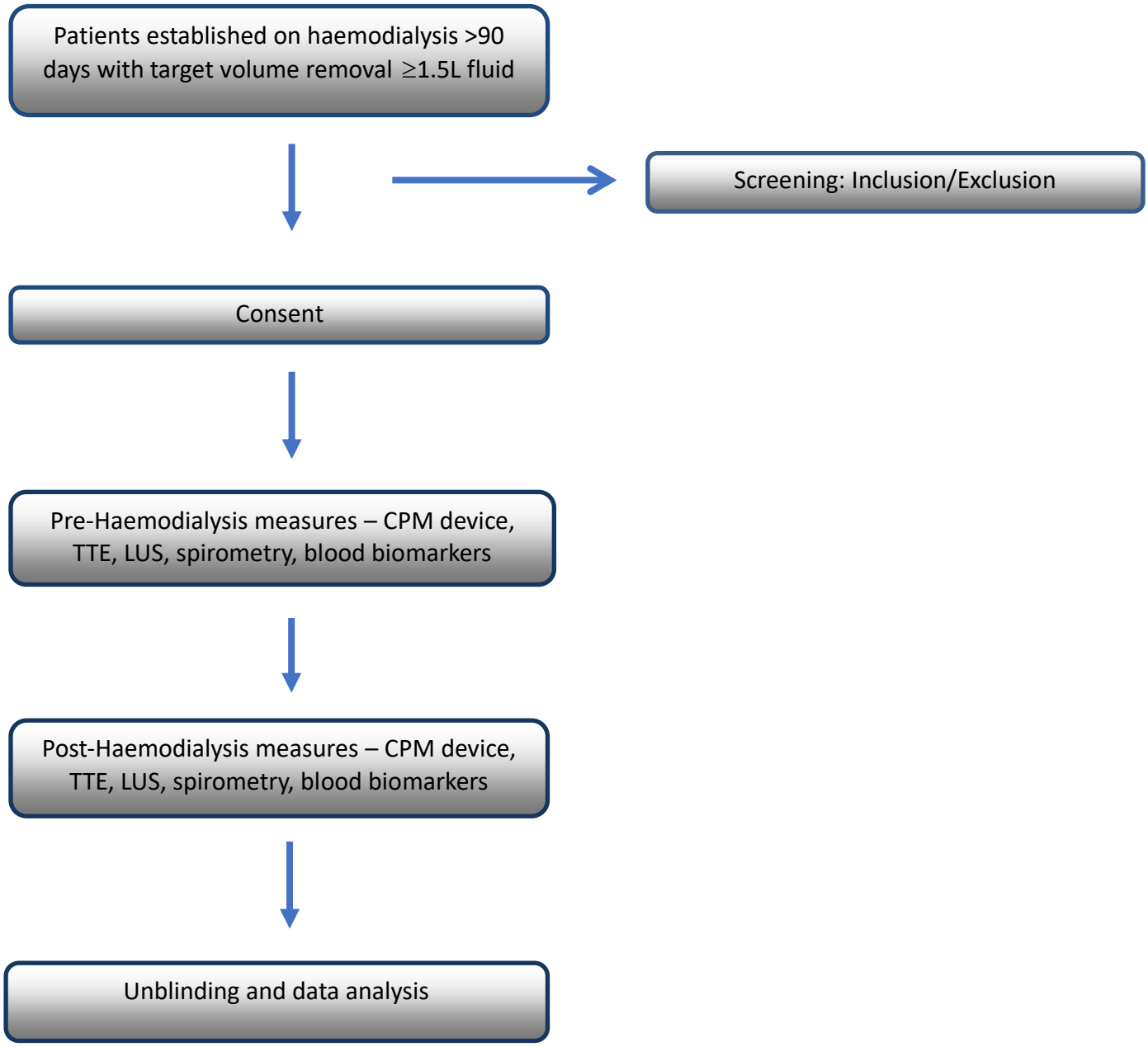
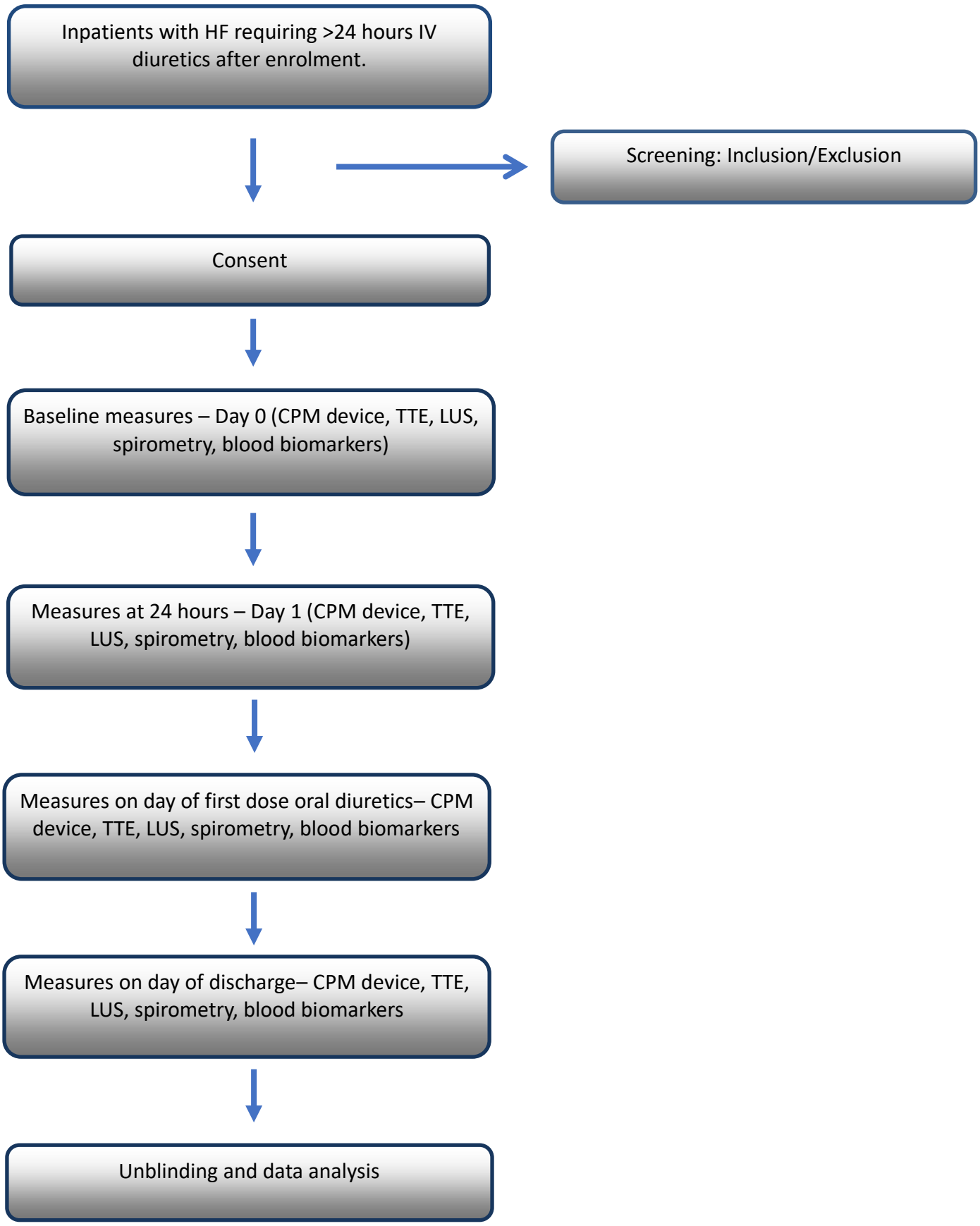


Figure 4-3 Cohort C Study Flow Chart



Patients who were discharged on the day of assessment were phoned within 48 hours to ask about any delayed reaction at the site where the device was applied. If a reaction was reported, the patient was to attend for review at the place of their assessment.

The study schedule and collection of samples are summarised in **Table 4-1**.

Table 4-1 Schedule of Assessments

Study Procedure	Training Cohort	Cohort A Day of RHC	Cohort B Prior to haemodialysis	Cohort B After haemodialysis	Cohort C Day 0	Cohort C Day 1	Cohort C Transition to oral diuretics	Cohort C Day of discharge
Consent to inclusion in study	√	√	√		√			
Physical examination	√	√	√	√	√	√	√	√
Weight		√	√	√	√	√	√	√
Urine output/ fluid balance					√	√	√	√
Vital signs	√	√	√	√	√	√	√	√
Right heart catheterisation data		√						
Dialysis prescription			√					
Diuretic treatment administered		√			√	√	√	√
Clinical history	√	√	√		√			
Drug history	√	√	√		√			√
Blood sample-								
NT-proBNP		√	√	√	√	√	√	√
U+E*		√	√	√	√	√	√	√
FBC*		√	√	√	√	√	√	√
Lung ultrasound		√	√	√	√	√	√	√
Echocardiography		√	√	√	√	√	√	√
Spirometry		√	√	√	√	√	√	√
CXR- from admission					√			
ECG- from admission		√			√			
Application of CPM wearable device	√	√	√	√	√	√	√	√

*Completed as part of usual care and results were available on NHS electronic case record or clinical notes for entry into the study eCRF

4.6 Investigational device training

To comply with the manufacturer's instructions for use and minimise improper application of the wearable device, I received training from ADI on how to apply the device and troubleshoot for potential device malfunctions. This training occurred in virtual format prior to study commencement.

4.7 Unexpected findings

If an unexpected finding occurred during a patient assessment that was of clinical significance (eg left ventricular thrombus on echocardiography), the patient's care team were to be informed for appropriate follow up.

4.8 Definition of end of study

Training Cohort: end of study was determined by the completion of a CPM wearable device reading.

Cohort A: end of study was determined after a clinically indicated RHC was performed and when all study-related procedures had been made.

Cohort B: end of study was determined by the end of haemodialysis and when all study assessments had been completed.

Cohort C: end of study was determined by completion of the final study assessment.

4.8.1 Withdrawal Criteria

Patients did not undergo a study assessment if they acquired any of the exclusion criteria and the reason was documented in the eCRF. In the case of an exclusion issue being resolved (eg rate control of rapid atrial arrhythmia) the patient was eligible to undergo further study assessments if the patient agreed and the assessment was deemed to be appropriate by the study investigator and the clinical care team. Patients could withdraw from the study at any point if they wished to, with no implications for their ongoing medical care.

4.8.2 Discontinuation of study

All patients were able to discontinue participation in the study at any point without any impact on the medical care they were receiving.

4.9 Assessment and management of risk

In line with NHS GG&C standard operating procedures, a risk analysis was conducted by the Sponsor prior to commencement of the study to determine any anticipated risks including adverse events and degree of risk posed to participants. A process for monitoring and reporting device related serious adverse events was established.

4.9.1 Adverse event monitoring and safety reporting

Adverse events were categorised by seriousness, expectedness and whether they were device related or not. Categories of adverse events are listed in **Table 4-2**.

Table 4-2 Categories of Adverse Events

<table>
<tr><th>ADVERSE EVENTS</th><th>Non-Device Related</th><th colspan="2">Device or Procedure Related</th></tr>
<tr><td>Non-Serious</td><td>Adverse Event (AE)[a]</td><td colspan="2">Adverse Device Effect (ADE)</td></tr>
<tr><td rowspan="3">Serious</td><td rowspan="3">Serious Adverse Event (SAE)[b]</td><td colspan="2">Serious Adverse Device Effect (SADE)</td></tr>
<tr><td>Anticipated</td><td>Unanticipated</td></tr>
<tr><td>Anticipated Serious Adverse Device Effect (ASADE)</td><td>Unanticipated Serious Adverse Device Effect (USADE)</td></tr>
<tr><td colspan="4">[a] Includes all categories
[b] Includes all categories that are serious</td></tr>
</table>

The definitions list below was used as part of the monitoring process and adverse events reporting procedure during the study.

Table 4-3 Definitions of adverse event

Term	Definition
Investigational Medical Device (IMD)	Medical device being assessed for safety or performance in a clinical investigation.
Adverse Event (AE)	Any untoward medical occurrence, unintended disease or injury or any untoward clinical signs (including an abnormal laboratory finding) in subjects, users or other persons whether or not related to the IMD. Note 1: This definition includes events related to the investigational device.

	Note 2: This definition includes events related to the procedures involved.
Adverse Device Effect (ADE)	Adverse event related to the use of the IMD. Note 1: This included any adverse event resulting from insufficiencies or inadequacies in the instructions for use, the deployment, the installation, the operation, or any malfunction of the IMD. Note 2: This also included any event that was a result of a use error or intentional abnormal use of the IMD.
Serious Adverse Event (SAE)	Adverse event that: • led to a death, injury or permanent impairment to a body structure or a body function. • led to a serious deterioration in health of the subject, that either resulted in: o a life-threatening illness or injury, or o a permanent impairment of a body structure or a body function, or o in-patient hospitalization or prolongation of existing hospitalization, or o in medical or surgical intervention to prevent life threatening illness • led to foetal distress, foetal death or a congenital abnormality or birth defect Note 1: Planned hospitalization for pre-existing condition, or a procedure required by the clinical investigation plan, without

	a serious deterioration in health, was not considered a serious adverse event. Note 2: The term "life-threatening" in the definition of "serious" refers to an event in which the participant was at risk of death at the time of the event; it does not refer to an event which hypothetically might have caused death if it were more severe.
Serious Adverse Device Effect (SADE)	An adverse device effect that resulted in any of the consequences characteristic of a serious adverse event. SADE was also any event that may have led to these consequences if • suitable action had not been taken, or • intervention had not been made, or • if circumstances had been less fortunate Note 1: Anticipated SADE (ASADE) is an effect which by its nature, incidence severity or outcome had previously been identified in the clinical investigation plan, investigator's brochure or clinical investigation risk analysis.
Unanticipated Serious Adverse Device Effect (USADE)	Any serious adverse device effect on health or safety or any life-threatening problem or death caused by, or associated with a device, if that effect, problem, or death was not previously identified in nature, severity or degree of incidence in the clinical investigational plan, or any other unanticipated serious problem associated with the device that related to the rights, safety or welfare of the subject.

Device Deficiency (DD)	Inadequacy of the IMD related to its identity, quality, durability, reliability, safety or performance. This included malfunctions, use error, or inadequacy in the information supplied by the manufacturer.

4.9.2 Recording and Reporting of Device Deficiencies

All device deficiencies that resulted in an SAE or may have potentially resulted in a SAE if action had not been taken or if circumstances had been less fortunate were to be documented via the eCRF within 24 hours of the Investigator's knowledge of the event. Device deficiencies were reported from the date of first application of the device until 48 hours following removal of the device. All such device deficiencies were reportable to the Sponsor. The following specific events had to be recorded as device deficiencies within the eCRF as soon as possible for the purposes of monitoring the acquisition and transfer of data to ensure that processes were working as per the device specifications.

- Any failure of the CPM device to capture useable data from any position
- Any failure of data transfer between the CPM device and the study PC laptop

4.9.3 Assessment of Seriousness

An adverse event was considered serious if it:

- resulted in death
- was life threatening
- required hospitalization or prolongation of existing hospitalization
- resulted in persistent or significant disability or incapacity
- consisted of a congenital anomaly or birth defect

- required intervention to prevent one of the above

4.9.4 Recording and reporting of Serious Adverse Events

The primary focus of the clinical investigation was to assess the effectiveness of the CPM device and therefore safety reporting for CONGEST-HF was focused on events that may have been caused by the device rather than the participant's underlying medical condition. As the device was a diagnostic and monitoring device it was highly unlikely to have any impact on the participant's HF, or any other medical conditions they may have had at the time of entry to the study.

The collection of SAEs was limited to those occurring during the period of exposure to the device and excluded events that were expected to occur in patients with HF and associated cardiovascular disease as they were not relevant to the monitoring of safety for use of the device. SAEs were to be recorded within the eCRF if they occurred between the date of application of the device and the date the device was removed + 48 hours. All SAEs were to be recorded in the eCRF within 24 hours of first becoming aware of the event. Events were to be followed up until the event has resolved or a final outcome had been reached or until 30 days after the end of the clinical investigation.

The two main foreseeable events were the potential for (1) allergic reactions to the materials utilised in the manufacture of the device, whether these were localised dermatological reactions or more a widespread systemic reaction, and (2) an interaction with a pre-existing implanted device (eg pacemaker or defibrillator).

4.9.5 Monitoring for local skin reaction to adhesive

ADI had provided the information reported in **Table 4-4** within the Investigator's Brochure required by the MHRA. Axelgaard, the company who manufactured the hydrogel adhesive component, had never had an adverse event reported to the United States Food and Drug Administration. As the device readings were planned to be worn for up to 15 minutes (5 minutes per reading, 3 readings per visit) the risk of skin reaction posed to patients was expected to be very low.

Table 4-4 Wear time and adverse reaction experience in human studies conducted by the manufacturers prior to CONGEST-HF

Study type	Number of patients/subjects	Continuous skin contact duration per measurement (min)	Number of measurements per day	Number of days	Total Exposure Time for all subjects (min)	Adverse Events related to use of hydrogel/adhesive
Usability	5	5	2	7	350	None
Usability	2	5	2	1	20	None
Usability	15	5	2	1	150	None
Clinical	40	60	1	1	2400	None
TOTAL	62	NA	NA	NA	2920	-

4.9.6 Monitoring for cardiac implanted electronic device interaction

The second potential adverse event that was foreseen was an interaction between an existing, implanted device and the wearable CPM device. The main concern was that activation of the wearable device would cause electromagnetic interference (EMI) that could affect the

functionality of the implanted device (eg noise-related oversensing and under-pacing or inappropriate detection of an arrhythmia and consequent defibrillator therapy). ADI had conducted prior pre-clinical studies of EMI compatibility testing according to IEC 60601-1-2 Standard: Medical Equipment-Part 1-2: General Requirements for Basic Safety and Essential Performance, Collateral Standard: Electromagnetic Compatibility[276]. Bench testing demonstrated that the CPM wearable device posed a negligible risk of EMI to implanted devices including in Bluetooth Advertising Mode with extremely low EMC emissions[277]. While the risk of EMI was low, to mitigate any potential harm to a study participant, in any patient with an implanted device I monitored the implanted device electrogram activity in real-time with an implanted device programmer for any possible interaction between devices. I hold accreditation as a cardiac device specialist with the International Board of Heart Rhythm Examiners (IBHRE). If any interaction was observed the wearable device was to be removed immediately, the study assessment terminated and the participant was to be withdrawn from the study. Data regarding the implanted device type, manufacturer and leads were recorded at baseline in the eCRF.

4.9.7 Causality Assessment

The relationship between the use of the CPM device and the occurrence of each ADE was to be assessed and categorised. The presence of confounding factors, such as concomitant medication/treatment, the natural history of the underlying disease, other concurrent illness or risk factors were also to be considered.

The following categories of causality were used:

Causal Relationship	The serious event was associated with the device or with procedures beyond reasonable doubt when: • The event was a known side effect of the product category the device belonged to or of similar devices and procedures; • The event had a temporal relationship with the IMD use/application or procedures; • The event involved a body-site or organ that the IMD or procedures applied to or had an effect on; • The serious event followed a known response pattern to the IMD (if the response pattern was previously known); • The discontinuation of the device application and reintroduction of its use impacted on the serious event; • Other possible causes (e.g. an underlying or concurrent illness/ clinical condition or/and an effect of another device, drug or treatment) were adequately ruled out; • Harm to the participant was due to error in use; • In order to establish the relatedness, not all the criteria listed above had to be met at the same time.
Probably Related	• The relationship with the device seemed relevant and / or the event could not be reasonably explained by another cause, but additional information was to be obtained

Possibly Related	• An event where the relationship with the use of the device was weak but could not be ruled out completely. • Alternative causes were also possible (e.g. an underlying or concurrent illness/ clinical condition or/and an effect of another device, drug or treatment). • Cases where relatedness could not be assessed or no information was obtained were also to be classified as possible.
Unlikely Related	• The relationship with the use of the IMD did not seem relevant and/or the event was reasonably explained by another cause, but additional information could be obtained.
Not related	• The event was not a known side effect of the product category the device belonged to or of similar devices and procedures; • The event had no temporal relationship with the use of the device or the procedures; • The serious event did not follow a known response pattern to the device (if the response pattern was previously known) and was biologically implausible; • The discontinuation of device application and the reintroduction of its use did not impact on the serious event; • The event involved a body-site or an organ not expected to be affected by the IMD or procedure;

	• The serious event could be attributed to another cause (e.g. an underlying or concurrent illness/ clinical condition, an effect of another device, drug, treatment or other risk factors); • Harms to the participant was not clearly due to use error; • In order to establish the non-relatedness, not all the criteria listed above had to be met at the same time

4.9.8 Assessment of Severity

Severity of an ADE was to be assessed and described using the following categories:

Mild	Awareness of a sign, symptom or event that was easily tolerated and transient in nature with minimal or no impairment to normal activity (acceptable).
Moderate	Moderate symptoms that were poorly tolerated, sustained, interfered with normal activity and required medical attention (disturbing).
Severe	Symptom(s) that required intervention, and where activities of daily living were significantly altered (unacceptable).

4.9.9 Assessment of expectedness

Any confirmed SADE was to be assessed by the Chief Investigator and/or Sponsor against the approved CPM device investigator's brochure and the clinical investigation plan to determine the expectedness of the event.

4.9.10 Reporting to the MHRA

The Sponsor was responsible for reporting to the MHRA. The following events were considered reportable events:

- any SAE
- any device deficiency that might have led to a SAE if:
    - suitable action had not been taken or
    - intervention had not been made or
    - if circumstances had been less fortunate
- new findings/updates in relation to already reported events.

An SAE or SADE which represented an imminent risk of death, serious injury, or serious illness and that required prompt remedial action was to be reported immediately, but not later than 2 calendar days after awareness by the Sponsor. Any other reportable events as described above were to be reported within 7 calendar days following the date of awareness by the Sponsor.

4.9.11 Reporting to the REC

All USADEs were to be submitted to the REC within 15 working days of the Chief Investigator (or designee) becoming aware of the event.

4.9.12 Data Monitoring Committee (DMC)

The anticipated risks to participants posed by the CPM device and this clinical investigation were low. Therefore, a formal DMC was not convened. To ensure adverse events were reviewed by persons independent to the research investigators, the AEs, SAEs, and SADEs reports were to be sent to and reviewed by two independent physicians. The Study Steering Committee (SSC) periodically reviewed safety data.

4.10 COVID- 19 mitigation

The study design aimed to minimize the risk of COVID-19 infection to patients and healthcare staff.

- All study assessments were conducted on participants who were already attending or admitted to hospital to receive care for HF or dialysis.
- The study assessments were conducted by one investigator (me), the clinical research fellow. Minimizing the number of researchers having patient contact aimed to reduce the risk of infection transmission from multiple sources.
- Patients were screened before an assessment for signs and symptoms of COVID-19 infection such as fever, new cough, sore throat, radiographic consolidation. Patients with suspected COVID-19 infection were temporarily removed from the study until a negative COVID-19 status was confirmed.
- Patients with confirmed COVID-19 infection were excluded from the study.
- COVID-19 infection of an active participant in the study was considered a SAE with reporting to the Sponsor accordingly.
- Contact tracing of COVID-19 confirmed cases was conducted and isolation implemented in accordance with NHS GGC guidelines and procedures

- If I developed features consistent with COVID-19 infection, isolation was implemented as per NHS GGC guidelines and procedures. In this event, the Sponsor was informed given the potential need to reschedule study assessments.
- A second clinical research fellow, Dr Joanna Osmanska, was added to the Delegation Log and trained in using the wearable device in case I contracted COVID-19 and required cover.
- Strict infection control procedures were followed before, during and after every assessment.
- Bacterial viral filters provided a high degree of protection from infection transmission during spirometry. A new filter was used for each tidal volume assessment and used filters were discarded.
- Devices (CPM wearable devices, spirometer, echocardiogram) were cleaned using medical standard alcohol agents before and after use to reduce the risk of viral transmission.

4.11 Statistics and Study Data Analysis

4.11.1 Statistical analysis

The study had a Statistical Analysis Plan, which was authored by the Study Statistician (Prof Alex McConnachie) and agreed by the investigators before the final analysis. The statistical analyses for each cohort are detailed further in **Chapters 5, 6 and 7**. No interim analysis was performed and the study analysis began when the investigators agreed to lock the database after all study data had been collected and tested. ADI had no role in the statistical analyses. Any further analyses beyond the statistical analysis plan were conducted by myself or in

collaboration with Dr Atefeh Talebi, Clinical Trials Medical Statistician at the University of Glasgow.

Apart from the Rhythm parameter, all the CPM device parameters provided continuous data. The main study analyses examined the correlation between these continuous data and clinical measures. A correlation tests the strength of association between two variables. When the relation between two variables is represented as a scatter plot (as in the Results chapters 5 - 7) Pearson's correlation coefficient provides a quantification of the degree of data point scatter around a line and provides a measure of association that does not imply any dependence of one variable on the other (unlike regression analysis where one variable is the dependent and the other is explanatory). Several assumptions regarding the underlying distribution of the data are made when analysing such a correlation between two continuous variables. It is assumed that the variables are independent to each other, that the *y* variable is normally distributed for each value of the *x* variable and that the *x* variable is normally distributed for each value of the *y* variable (bivariate normal distribution). It is also assumed that there is a linear relationship between the mean of the *y* values and each corresponding x[278]. As the CONGEST-HF study was an exploratory investigation, it was not clear whether relationships between the device and other clinically obtained continuous variables (eg LUS B-lines or NT-proBNP) would be linear or non-linear or curvilinear. As will be detailed in the cohort specific chapters of this thesis (Chapters 5 - 7), there were some missing study visit data due to patients either dying or being excluded and there were some outlier values within some of the data. The number of patients recruited was also less than originally planned. As there was uncertainty about whether all of the assumptions underlying a Pearson's correlation coefficient held for the study data, the alternative

Spearman's correlation was performed. Spearman's correlation allowed non-linear relations between variables to be examined and as a non-parametric test it accounted for non-normality of data due to smaller sample sizes or missing data and outlier values. In this thesis Spearman's correlation coefficient is denoted by the term "r_{sp}". The strength of the correlation ranges from values of -1 to +1. A negative correlation value describes an inverse correlation. Cut-off points have been described to grade the strength of the correlation, with coefficients of -1 or +1 being the strongest linear associations, and a coefficient of 0.00 – 0.19 being a negligible correlation, 0.20 – 0.39 a weak correlation, 0.40 – 0.59 a moderate correlation, 0.60 – 0.79 a strong correlation, 0.80 – 1.00 a very strong correlation[279].

No adjustment was made for multiple analyses. Multiplicity in a study such as CONGEST-HF could lead to a potential increase in the type I error rate due to multiple testing of the correlation between a broad number of device and clinical congestion measures at several different study intervals[280]. However, I did not apply any adjustments for multiple testing because the study was exploratory, investigating if the device was able to detect shifts in congestion in patients whose clinical status was dynamic. The results from these exploratory analyses were not intended to be the definitive examination of whether the device would reduce hospitalizations for HF. Instead, the analyses in the CONGEST-HF study were intended to provide hypothesis generating data that would ultimately support the conduct of a confirmatory, clinical endpoint-driven trial investigating the CPM device.

4.11.2 Primary analyses

Cohort A: Spearman correlation coefficient (r_{sp}) between diastolic heart sound energy (S3) measured by the CPM wearable device and PCWP on invasive RHC.

Cohort B: Spearman correlation coefficient between lung fluid and change in lung fluid (thoracic impedance) measured by the CPM wearable device and B-lines and change in B-lines on LUS and volume of fluid removed by dialysis

Cohort C: Spearman correlation coefficient between lung fluid and heart sound energy and change in lung fluid and heart sound energy measured by the CPM wearable device and B-lines and change in B-lines on LUS and change in weight.

4.11.3 Secondary analyses

Cohort A: Spearman correlation coefficient between measures derived by the CPM wearable device with:

- Measures derived from RHC including RA and RV pressure, PA pressure, PA oxygen saturation and Cardiac Output
- Measures derived from echocardiography
- Number of B lines on LUS
- Tidal Volume on pulmonary function testing
- Signs and symptoms of congestion

Cohort B: Spearman correlation coefficient between measures derived by the CPM wearable device and the following parameters before and after haemodialysis:

- Echocardiography measures
- Tidal volume on pulmonary function testing
- Signs and symptoms of congestion

Cohort C: Spearman correlation coefficient between measures derived by the CPM wearable device and measures of congestion during treatment for heart failure with IV diuretics:

- Echocardiography
- Tidal volume on pulmonary function testing
- Signs and symptoms of congestion

4.11.4 Exploratory analyses

Cohort A, B and C: Spearman correlation coefficient between congestion measured by the CPM wearable device and;

- Concentration of NT-ProBNP
- Concentration of MR-proANP
- Haemoconcentration measured by Haematocrit

Cohort A, B, C: Spearman correlation coefficient between congestion measured by the CPM wearable device and LV GLS on echocardiography.

Cohorts A, B, C: Spearman correlation coefficient between CPM device-measured heart rate and clinical examination heart rate, and the relation between the CPM device assessed heart rhythm parameter and the presence of an irregular heart rhythm on clinical examination.

In the event of missing data (eg patient exclusion or inability to complete an assessment) that patient was to be excluded for that time point.

4.11.5 Sample size

Cohort A required assessment at a minimum of one single time point, and a sample size of 20 patients were to be recruited, giving 80% power to detect a correlation of 0.6 at 5% statistical significance. This number of patients was in line with cohort sizes in previous studies validating implantable haemodynamic monitor pressures readings (CardioMEMS and Chronicle) with right heart catheterisation values[56,281]. Cohorts B and C required multiple assessments per patient, so I aimed to recruit 40 patients into each cohort, giving protection against missing outcome data, while ensuring at least the same level of statistical power as for Cohort A.

4.12 Data Handling

4.12.1 Case Report Forms

Anonymised patient data was recorded in the study database via entries to individual electronic case report forms (eCRFs). Data included height, weight, gender, age, comorbidities, current medications, past medical history, laboratory results, medical imaging data, procedural data, symptoms and physical examination findings. Each patient was allocated a unique study identifier and no patient identifiable information was kept in the study database. Access to the eCRF was restricted, via a study-specific web portal, and only authorized site-specific personnel were able to make entries to the patients' data via the web portal.

The study database was hosted by the Clinical Trials Unit (CTU) at the Robertson Centre for Biostatistics (RCB), Glasgow. Data integrity was assured by strictly controlled procedures, including secure data transfer procedures. The RCB has an ISO 9001:2008 quality management system and ISO 27001:2013 for Information Security, and is regularly inspected against the standards by the British Standards Institution.

4.12.2 Source Data

Data entered into the eCRF were obtained from source documents, including medical notes, medical images and measurements, laboratory results, ECGs. Source documents were not removed from study sites. Hard drives were held securely at the study sites with access provided to the relevant researchers only. Site files and study materials were archived at the end of study.

4.12.3 Imaging review

To ensure the quality of the LUS assessments, 10% of the total studies were reviewed by an independent investigator as part of a core lab process. The sample group were randomly selected studies. Images were saved using study identifiers only and onto secure hard drives at the end of each assessment. I hold accreditation with the ESC/EACVI in transthoracic echocardiography.

4.13 Study Management

4.13.1 Study Steering Committee (SSC)

A SSC oversaw the running of the study and ensured that it was conducted in accordance with the principles of Good Clinical Practice and ISO14155:2020 and the relevant regulations. The SSC had no concerns regarding the study's design or operations.

4.13.2 Study Management Group (SMG)

A SMG convened during the study consisting of representatives from the NHS Sponsor and the UOG including the Chief Investigator, co-investigators, the clinical research fellow and the Study Manager. The role of the group was to monitor all aspects of the conduct and progress of the study, to ensure that the CIP was adhered to and take appropriate action to safeguard participants and the quality of the study itself.

4.13.3 Study monitoring and audit

Study monitoring visits were conducted by Dr Margaret Fegen, NHS GGC Monitor. The level of monitoring was based on the outcome of the completed monitoring risk assessment. A monitoring plan was approved by the NHS GG&C Research Governance Manager / Academic Lead Clinical Trial Monitor. As standard, monitoring visits covered site file review, review of Informed Consent Forms (ICFs), Source Data Verification (SDV) and SAE review as per the monitoring plan objectives.

4.13.4 Management of clinical investigation plan deviations

Clinical investigation plan deviations were recorded. Each violation was reported by the study investigator to the Sponsor within no less than 3 days of becoming aware of the violation. The Sponsor had responsibility for notifying the REC and MHRA of such violations.

5. CHAPTER FIVE. A Study of the non-invasive CardioPulmonary Management (CPM) device in patients with advanced heart failure

5.1 Introduction

Patients with advanced HF are people who are receiving the maximum tolerated, conventional treatment options but yet remain highly symptomatic or who have an expected poor prognosis[282]. Standard treatments include guideline-directed medical therapy (RAAS inhibition, beta-blockers, mineralocorticoid receptor antagonists, sodium glucose co-transporter 2 inhibitors), diuretics and device therapy (implantable cardioverter defibrillators and cardiac resynchronization therapy). A select number of patients with advanced HF and without contra-indications may be offered cardiac transplantation and / or left ventricular assist device therapy to improve their prognosis and relieve symptoms[283,284].

RHC provides valuable haemodynamic data upon which candidacy for advanced HF therapy can be decided. As described in the Introduction, PCWP reflects left atrial pressure and in turn left ventricular end-diastolic pressure (in the absence of significant mitral valve disease such as mitral stenosis). RHC is the gold-standard measure for assessing filling pressures and congestion. Other RHC values, in particular mean pulmonary artery pressure and right atrial pressure also reflect the degree of congestion a person is experiencing but these measures may be influenced by the presence and severity of pulmonary disease rather than being specific to left ventricular impairment. RHC has been used in previous studies of implantable cardiac devices (CardioMEMS and Chronicle) to validate the haemodynamic data obtained by the device[56,281]. In this study I examined whether the CPM device measures correlated

with invasive haemodynamics measured by RHC at a single time point, as well as lung ultrasound, spirometry, clinical signs and symptoms, echocardiography, ECG and biomarkers of congestion.

5.2 Methods

Patients with advanced HF receiving treatment at the Scottish National Advanced Heart Failure Unit, GJNH were recruited into the study. The inclusion / exclusion criteria were outlined in **Chapter 4**.

5.2.1 Study procedures

5.2.1.1 Right heart catheterization

All other study procedures were performed before the RHC. The CPM device readings were taken directly before the RHC. Written, informed consent was obtained from all patients prior to performing the RHC. Patients lay supine on a dedicated, procedure table. A sterile field was prepared and 1% lidocaine injected into the subcutaneous tissue of the neck. Using ultrasound, right internal jugular vein access was secured and a 7 French Cordis sheath inserted. Patients were monitored using a standard 3 lead ECG, oxygen saturations and automated blood pressure cuff. A 7 French swan-gantz catheter was flushed and zero set at mid-thoracic level. The swan-gantz catheter was advanced through the sheath sequentially through the chambers of the heart with measures obtained at end-expiration if tolerated. Pressures were recorded in the following order: right atrium, right ventricle, PCWP, pulmonary artery pressures. Cardiac output was then measured using the thermodilution method with injection of 10mls of cold saline (kept in a refrigerator until thermodilution

injection) and a pulmonary artery oxygen saturation was taken (used to calculate cardiac output using the Fick method). The swan-gantz catheter was then removed along with the jugular sheath. Pulmonary vascular resistance, systemic vascular resistance and the transpulmonary gradient were calculated.

5.2.1.2 Other study procedures

CPM device readings and data transfer, echocardiography, lung ultrasound, spirometry, blood phlebotomy and analysis were all carried out in accordance with the CONGEST-HF study standard operating procedures (**Chapter 4 and Appendix**). The blood biomarkers NT-proBNP and MR-proANP were analysed in batch at the end of the study with the samples obtained from all three cohorts in the CONGEST-HF study. NT-proBNP (e411, Roche Diagnostics, UK) and MR-proANP (BRAHMS Kryptor, Thermofisher Scientific, UK) were measured on automated platforms using the manufacturers reagents, calibrators and quality control materials. The central laboratory (GlasBRU, University of Glasgow) conducting the measurements participated in the National External Quality Assurance Scheme (NEQAS) for the measurement of NT-proBNP.

5.2.1.3 Physical examination and clinical symptoms

As for all cohorts, I examined every patient for signs of congestion and took a symptoms-based history. The JVP was examined at 45 degrees in adequate lighting. The JVP was recorded in centimetres in patients in whom the JVP was visible more than 4 cm above the sternal angle (angle of Louis). Presence or absence of peripheral oedema was recorded, as was presence or absence of pulmonary rales.

I recorded the following symptoms of heart failure: dyspnoea on the EVEREST congestion scale (0 = none, 1 = seldom, 2 = frequent, 3 = continuous)[17]; New York Heart Association (NYHA) class (1 = no limitation, 2 = mild symptoms on ordinary activity, 3 = significant limitation on ordinary activity, 4 = severely limited, symptoms at rest); and presence (or not) of bendopnoea or orthopnoea.

5.3 Statistical Analyses

Continuous variables were summarised using the mean and standard deviation (SD) or median with inter-quartile ranges (IQR) depending on the normality of the data. Categorical variables were summarised with frequencies and percentages. Patient-individual Spearman correlations were used to determine the correlations between device measurements and clinical study parameters that were continuous variables. Scatterplots graphically represent the correlations. Relations between continuous and categorical variables were analysed using Mann-Whitney-Wilcoxon tests or Kruskal-Wallis tests as appropriate. A p value <0.05 was considered statistically significant. Analyses were performed using STATA version 18 (College Station, Texas, USA).

5.4 Results

5.4.1 Study population

20 people were recruited into the study between 6th December 2021 and 13th April 2022, of whom 11 (55%) were ambulatory outpatients undergoing elective RHC. The remaining 9 (45%) were inpatients on the advanced HF unit, undergoing evaluation for urgent advanced HF treatment (transplantation or mechanical circulatory support). The people recruited into

the study were representative of patients considered eligible for such therapies, in that they were young (mean age 55.0 ± 9.35 years), non-obese, had preserved renal function but severely impaired LV systolic function. While the cohort included outpatients, these people had advanced HF and were highly symptomatic (65% were NYHA class III/IV) despite high rates of guideline directed medical therapy. 12 (60%) of people had an implantable device, including 11 ICDs and 1 CRT-defibrillator.

Table 5-1 Baseline characteristics of people enrolled into Cohort A of the CONGEST-HF study

	Cohort A
N = (%)	20
Male sex (%)	14 (70.0)
Age (years)	55.0 ± 9.35
Race (%)	
White	20 (100)
Black	-
Asian	-
Other	-
BMI (kg/m^2)	27.1 ± 3.9
Medical History (%)	
Hypertension	1 (5.0)
Diabetes	3 (15.0)
AF on baseline ECG	4 (20.0)
History of any AF	9 (45.0)

MI	4 (20.0)
Stroke	1 (5.0)
COPD	1 (5.0)
LVEF (%)	30 ±11
NYHA Class (%)	
I	-
II	7 (35.0)
III	12 (60.0)
IV	1 (5.0)
Symptoms/signs (%)	
Dyspnoea	19 (95%)
Orthopnea	9 (45.0)
PND	3 (15.0)
Fatigue	20 (100)
Bendopnea	13 (65.0)
Peripheral oedema	4 (20.0)
Systolic BP (mmHg)	103 ± 13
Heart rate (bpm)	75 ± 19
Respiratory rate (per min)	16 ± 2
Chest circumference (cm)	108 ± 10
Duration of HF	
<1 year	3 (15.0)
1 – 5 years	7 (35.0)

>5 years	10 (50.0)
Ischaemic aetiology (%)	6 (30.0)
Prior HF Hospitalization (%)	11 (55.0)
HF Hospitalization within previous 6 months (%)	3 (15.0)
NT-proBNP (pg/ml)	2116 (784, 4341)
MR-proANP (pmol/L)	327.32 (150, 492)
eGFR (mL/min/1.73m^2)	58.5 (45, 76.5)
Haematocrit (L/L)	0.38 ± 0.56
ECG – sinus (%)	13 (65.0)
ECG – AF (%)	4 (20.0)
ECG – Paced rhythm (%)	4 (20.0)
Baseline treatment (%)	
Inotropes	1 (5.0)
Loop diuretic	18 (90.0)
Thiazide / Thiazide-like diuretic	1 (5.0)
ACE inhibitor or Angiotensin Receptor Blocker	4 (20.0)
Sacubitril / Valsartan	12 (60.0)
Beta-blocker	17 (85.0)
MRA	15 (75.0)
SGLT2 inhibitor	13 (65.0)

Digoxin	2 (10.0)
Any implanted device	12 (60.0)
ICD	11 (55.0)
CRT-D	1 (5.0)
CRT-P	0 (0.0)
Pacemaker	0 (0.0)
Loop recorder	0 (0.0)

ACE = angiotensin converting enzyme; AF = atrial fibrillation; BMI = body mass index; COPD = chronic obstructive pulmonary disease; CRT-D = cardiac resynchronization therapy-defibrillator; CRT-P = cardiac resynchronization therapy-pacemaker; ECG = electrocardiogram; eGFR = estimated glomerular filtration rate; HF = heart failure; ICD = implantable cardioverter defibrillator; LVEF = left ventricular ejection fraction; MI = myocardial infarction; MRA = mineralocorticoid receptor antagonist; MR-proANP = mid regional pro-atrial natriuretic peptide; NT-proBNP = n-terminal pro-B type natriuretic peptide; NYHA = New York Heart Association; PND = paroxysmal nocturnal dyspnoea; SGLT2 = sodium glucose co-transporter 2.

5.4.2 Invasively measured haemodynamics

RHC was performed in all 20 patients. One patient did not have the PA saturation analysed due to the sample clotting. There were no other missing invasive haemodynamic data. **Table 5-2** summarizes the invasive haemodynamic data obtained at catheterisation. The median PCWP [11.5 mmHg (7.5 - 21)] and RA [4 mmHg (2 – 8)] values indicate that the cohort were,

on average, euvolaemic. Cardiac output by thermodilution was mildly reduced [4.1 L/min (3.5 – 4.9)] and consistent with the measures obtained when cardiac output was calculated using the Fick equation. Intra-pulmonary pressures were within normal limits (mean PA pressure 19.5 mmHg (14.5 - 28) and PVR 1.7 Wood Units (1.3 – 2.4)].

Table 5-2 Invasive haemodynamic data [median (IQR)] obtained at right heart catheterization

Parameter	
Right Atrium (mmHg)	4.0 (2.0 – 8.0)
Right Ventricle (mmHg)	
Systolic	33.5 (26.0 – 44.0)
Diastolic	1.0 (0.0 - 5.0)
Mean	13.0 (10.0 – 20.5)
Pulmonary Artery (mmHg)	
Systolic	29.0 (24.5 – 41.5)
Diastolic	12.0 (7.5 - 19.0)
Mean	19.5 (14.5 - 28.0)
Pulmonary Capillary Wedge Pressure (mmHg)	11.5 (7.5 - 21.0)
Thermodilution	
Cardiac Output (L/min)	4.1 (3.5 – 4.9)
Cardiac Index [(L/min)/BSA]	2.1 (1.9 – 2.5)
Fick equation	
Cardiac Output (L/min)	4.1 (3.1 – 4.9)
Cardiac Index (L/min)	2.1 (1.9 – 2.7)

Transpulmonary gradient	8.0 (6.0 - 9.0)
Pulmonary Artery Saturation (%)	65.0 (58.0 - 69.0)
Pulmonary Vascular Resistance (Wood Units)	1.7 (1.3 – 2.4)
Systemic Vascular Resistance (Dynes)	1430.5 (1200.0 – 1694.5)

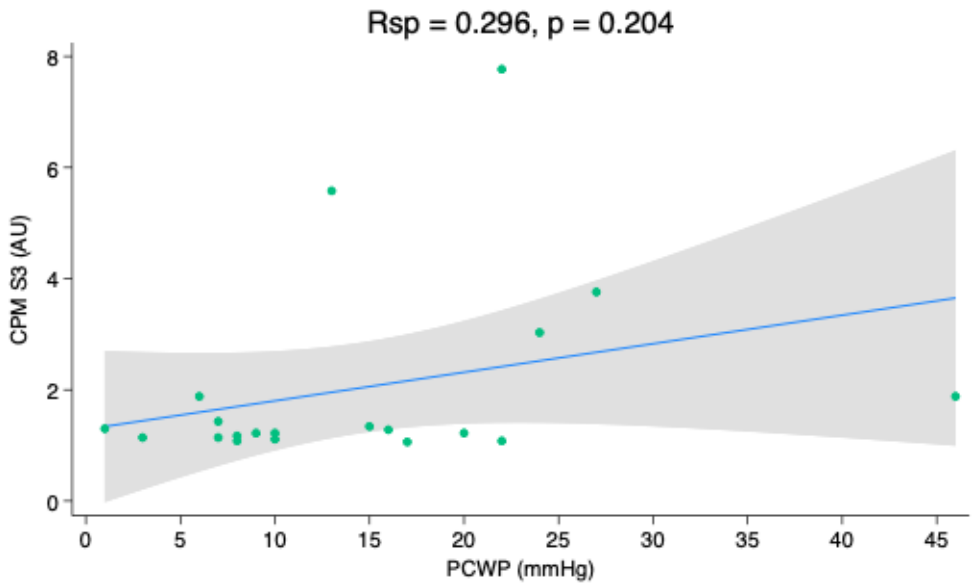
5.4.3 CPM device measures

Measured at a single time point, the median CPM device S3 was 1.25 AU (1.14 – 1.88), thoracic impedance was 77.6 ohms (57.9 – 117.0) and tidal volume was 0.8 ohms (0.5 – 1.3).

5.4.4 Primary analysis

In Cohort A, device-measured S3 and PCWP obtained at a single time-point were not significantly correlated (r_{sp} = 0.296, p=0.204).

Figure 5-1 Scatter plot of the correlation between CPM device S3 and PCWP



5.4.5 Secondary analyses

5.4.5.1 Correlations between CPM device-measures and invasively measured haemodynamics

On analysis of additional RHC measures in Cohort A, PVR on RHC was significantly correlated with device thoracic impedance (r_{sp} = -0.472, p = 0.036). Cardiac index (calculated using the Fick equation) was inversely correlated with tidal volume measured by the CPM device (r_{sp} = -0.47, p = 0.043). There were no other correlations identified between the CPM device and RHC measures (**Table 5-3**).

Table 5-3 Spearman correlations (r_{sp}) between RHC parameters and CPM device measured S3, thoracic impedance and tidal volume

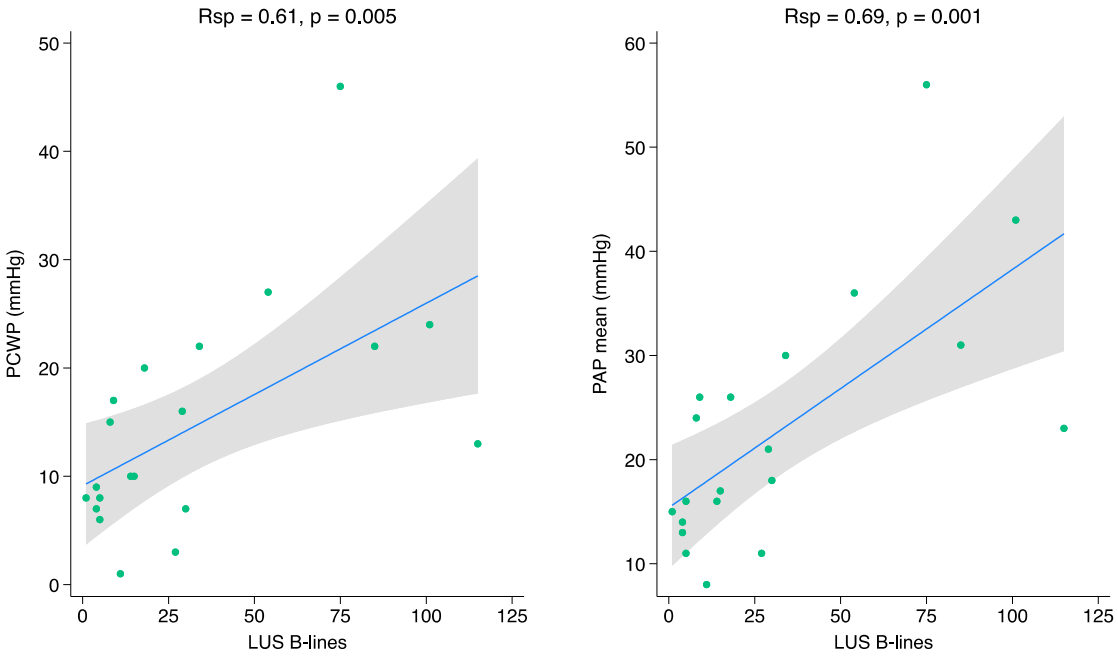
Cohort	RHC Parameter	CPM device S3 r_{sp} =	p =	CPM device Thoracic Impedance r_{sp} =	p =	CPM device Tidal Volume r_{sp} =	p =
A	Cardiac Output (Thermodilution)	-0.225	0.338	0.291	0.211	-0.296	0.204
A	Cardiac Index (Thermodilution)	-0.269	0.250	0.250	0.285	-0.238	0.309
A	Cardiac Output (Fick)	-0.290	0.227	0.316	0.185	-0.428	0.068
A	Cardiac Index (Fick)	-0.396	0.093	0.355	0.135	-0.471	0.043
A	PA pressure – mean	0.293	0.208	-0.213	0.364	0.302	0.195
A	PA pressure – systolic	0.248	0.288	-0.074	0.755	0.217	0.355
A	PA pressure – diastolic	0.350	0.130	-0.222	0.343	0.361	0.117
A	PA saturation	-0.291	0.225	0.329	0.167	-0.332	0.164
A	RA pressure	0.041	0.863	0.159	0.499	-0.121	0.610
A	Pulmonary Vascular Resistance	0.253	0.279	-0.472	0.036	0.398	0.083
A	Systemic Vascular Resistance	0.314	0.176	-0.248	0.289	0.290	0.214
A	PCWP	0.296	0.204	-0.082	0.729	0.270	0.248

5.4.5.2 Correlations between invasively measured haemodynamics and LUS B-lines

The median (IQR) number of B-lines on 8-zone LUS was 17 (7 - 44). In order of magnitude, the median number of B-lines per zone was; zone 8 [4 (0 - 9)], zone 7 [4 (0 - 7)], zone 3 [3, (0 - 8)], zone 2 [2.5 (1 – 8)], zone 4 [1 (0 - 5)], zone 6 [0 (0 - 4)], zone 5 [0 (0 - 2)], zone 1 [0 (0 - 1)]. LUS was performed in all 20 patients, with no missing data.

B-lines were significantly correlated with mean PCWP (r_{sp} = 0.61, p=0.005) and mean PA pressure (r_{sp} = 0.69, p = 0.001) on RHC (**Figure 5-2**).

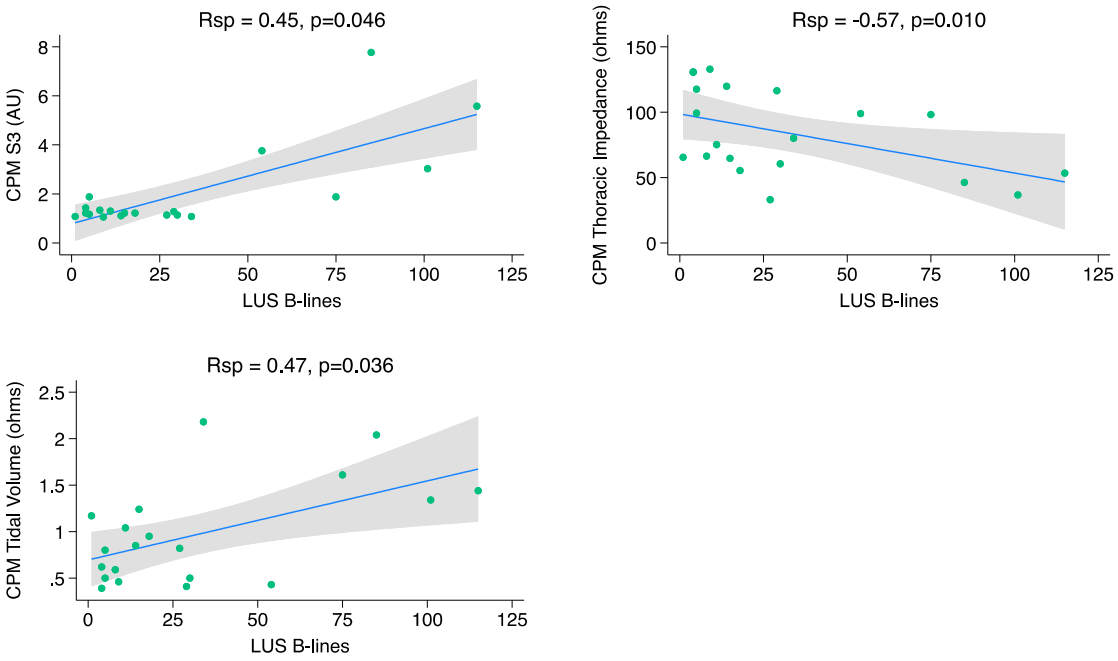
Figure 5-2 Scatter plots of the correlation between LUS B-lines and RHC measures



5.4.5.3 Correlation of CPM device measures and LUS B-lines

B-lines on LUS were significantly correlated with CPM S3 (r_{sp} = 0.453, p=0.046), CPM thoracic impedance (r_{sp} = -0.57, p=0.010) and CPM tidal volume (r_{sp} = 0.474, p=0.036).

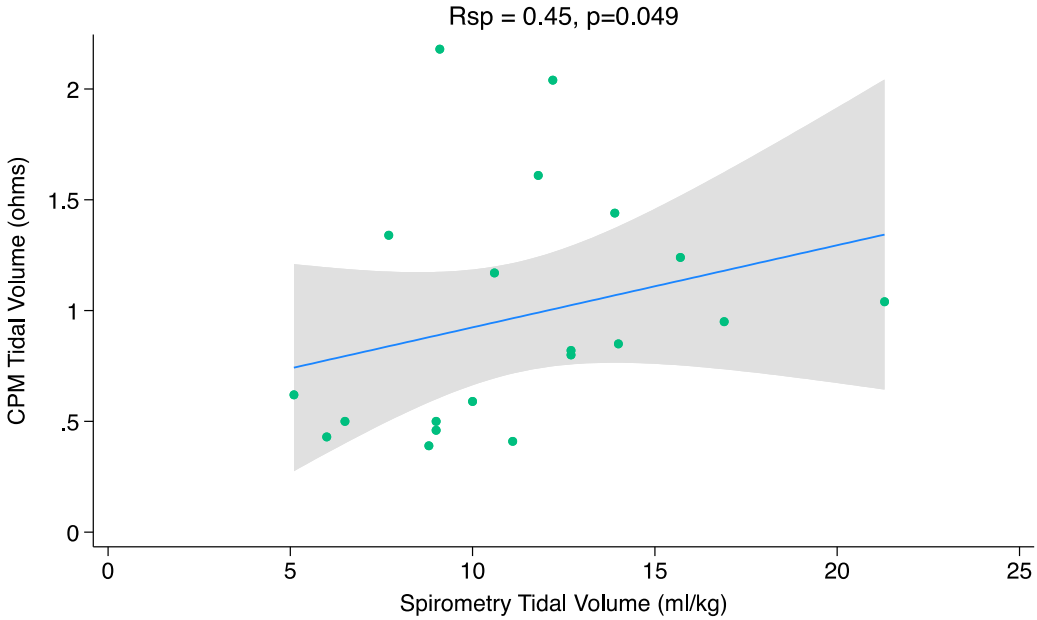
Figure 5-3 Scatter plots of the correlation between CPM device measures and LUS B-lines



5.4.5.4 Correlation between CPM device tidal volume and spirometry tidal volume

Tidal volume by bedside spirometry was obtained from all patients. The median (IQR) tidal volume was 10.8 ml/kg (8.9 – 13.3). CPM device tidal volume and spirometry tidal volume were significantly correlated (R_{sp} = 0.45, p = 0.049) (**Figure 5-4**).

Figure 5-4 Scatter plot of the correlation between CPM device tidal volume and tidal volume by spirometry



5.4.5.5 Correlation of invasive haemodynamics with echocardiographic measures

All patients underwent echocardiography. Due to poor imaging windows or factors such as atrial fibrillation, the following variables had missing data: E/e' ratio, n = 2; E/A ratio, n = 7, PVAT, n = 1; LV GLS, n = 2; LVOT VTI, n = 1; IVC diameter, n = 3; MV inflow deceleration, n = 2. **Table 5-4** summarizes the echocardiographic data obtained. As invasive haemodynamic data were also available in this cohort, the echocardiographic data were correlated with the most appropriate RHC measures. Cardiac output values in **Table 5-4** are those obtained by thermodilution, and the correlations reported below were consistent with those between cardiac output by the Fick method and echocardiographic measures.

Table 5-4 Spearman correlation of invasive haemodynamics with echocardiography measures

Parameter	Value	RHC parameter	Correlation Coefficient	p Value
LVEF (%)	30.3 ± 10.9	Cardiac Output (L/min)	0.26	0.258
Cardiac Output (L/min)	4.1 (3.0 – 5.1)	Cardiac Output (L/min)	0.53	0.026
E/e'	13.5 (9.3 – 21.8)	PCWP (mmHg)	0.35	0.152
TR vmax (m/s)	2.0 (1.2 – 2.4)	PA systolic (mmHg)	0.40	0.078
GLS (%)	-6.6 (-11.1 to -5.7)	Cardiac Output (L/min)	-0.38	0.118
E/A ratio (m/s)	1.6 (1.2 – 1.6)	PCWP (mmHg)	0.23	0.454
IVC diameter (mm)	17 (15 - 26)	RAP (mmHg)	0.54	0.026
LVOT VTI (cm)	17 ± 5.4	Cardiac Output (L/min)	0.21	0.396
PVAT (ms)	104 (83 - 128)	PVR (Woods Unit)	-0.31	0.191
LAVI (ml/m^2)	60.8 (44.5 – 73.6)	PCWP (mmHg)	0.76	<0.001
MV deceleration time (ms)	163 (128 - 206)	PCWP (mmHg)	-0.50	0.036

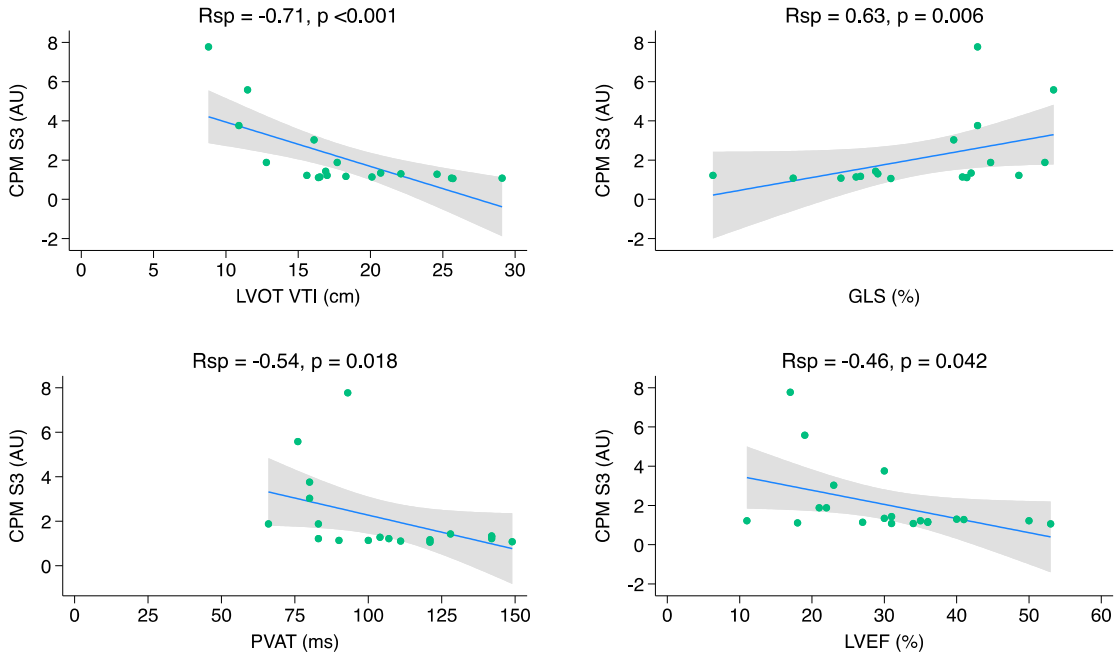
5.4.5.6 Correlation between CPM device and echocardiographic measures

In order of magnitude, LVOT VTI (r_{sp} = -0.714, p<0.001), LV GLS (r_{sp} = 0.626, p<0.001), PVAT (r_{sp} = -0.543, p=0.018), LVEF (r_{sp} = -0.460, p=0.042) were significantly correlated with CPM device S3, whereas the remaining echocardiographic parameters were not correlated (**Table 5-5, Figure 5-5**).

Table 5-5 Spearman correlations of CPM device S3 with echocardiographic measures

Cohort	Parameter	Correlation Coefficient	p =
A	LVOT VTI	-0.71	<0.001
A	LV GLS	0.63	0.006
A	PVAT	-0.54	0.018
A	LVEF	-0.46	0.042
A	E/A ratio	0.33	0.270
A	IVC diameter	0.13	0.624
A	MV inflow deceleration	-0.06	0.827
A	E/E' (average)	0.04	0.877
A	TR Vmax	0.03	0.901
A	LAVI	0.004	0.987

Figure 5-5 Scatterplots of correlations between CPM device S3 and echocardiographic measures



Correlations between echocardiographic measures and CPM thoracic impedance and CPM tidal volume were weaker than for the CPM S3 parameter. No significant correlations were identified between CPM thoracic impedance and any of the echocardiographic parameters (**Table 5-7**).

Table 5-6 Spearman correlations between CPM device thoracic impedance and echocardiographic measures

Cohort	Parameter	Correlation Coefficient	p =
A	E/E' (average)	-0.411	0.090
A	TR Vmax	0.107	0.651
A	E/A ratio	-0.383	0.194
A	PVAT	0.215	0.374
A	LV GLS	-0.053	0.834
A	LVEF	0.348	0.131
A	LVOT VTI	0.330	0.167
A	IVC diameter	0.374	0.138
A	LAVI	-0.28	0.225
A	MV inflow deceleration	-0.115	0.648

CPM device tidal volume was inversely correlated with LVEF (-0.54, p = 0.015) and no other echocardiographic measures (**Table 5-8**).

Table 5-7 Spearman correlations of CPM device tidal volume and echocardiographic measures

Cohort	Parameter	Correlation Coefficient	p =
A	E/E' (average)	0.34	0.172
A	TR Vmax	-0.29	0.208
A	E/A ratio	-0.02	0.957
A	PVAT	0.02	0.938
A	LV GLS	0.14	0.569
A	LVEF	-0.54	0.015
A	LVOT VTI	-0.19	0.436
A	IVC diameter	-0.28	0.915
A	LAVI	0.23	0.329
A	MV inflow deceleration	-0.17	0.498

5.4.5.7 Correlation between clinical examination and invasive measures on RHC

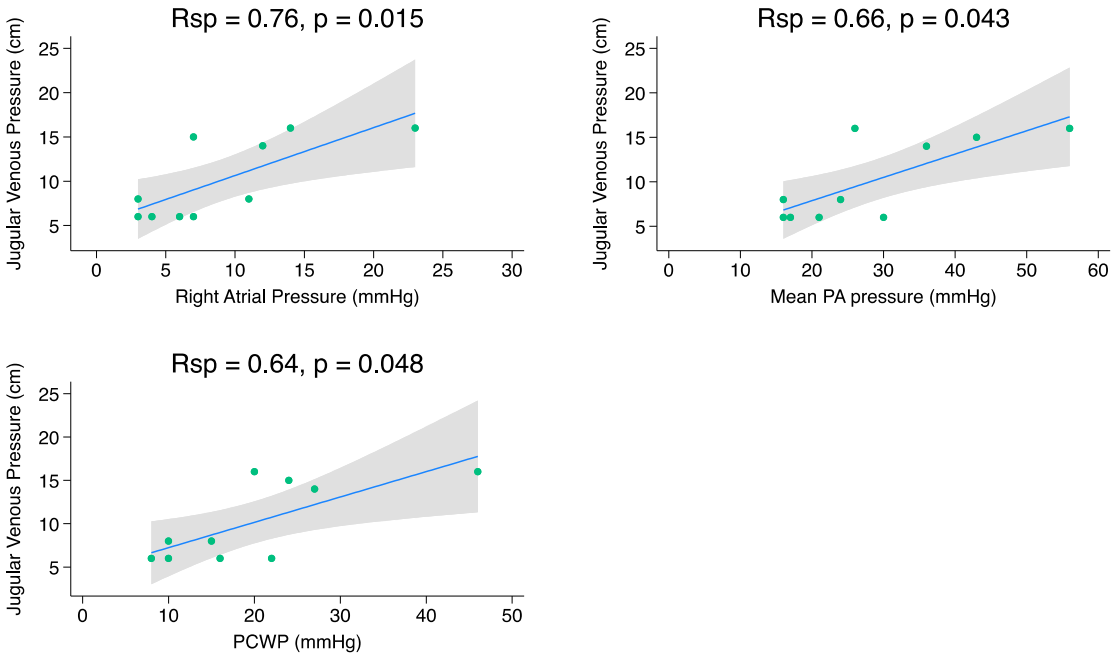
8 of 20 (40%) patients had a S3 heard on clinical auscultation of heart sounds. These 8 patients had a numerically greater, but not statistically different, PCWP than patients who did not have a S3 on clinical examination [19 mmHg (11 - 23) versus 10 mmHg (7 - 16), p = 0.130]. 6 of 20 (30%) patients had rales on auscultation. There was a clear trend towards higher PCWP, mean PA pressure and right atrial pressure on RHC in patients who had rales on examination compared with those people who did not, but the difference between groups did not reach statistical significance (**Table 5-9**). Peripheral oedema was detected in 4 of 20 (20%) of patients. In this advanced HF cohort, people with peripheral oedema, compared with those who did not have oedema, also had higher right atrial pressure, mean PA pressure and PCWP (**Table 5-9**).

Table 5-8 RHC values according to presence or absence of clinical signs of congestion

RHC	Clinical Parameter		p =
	Clinical S3 – yes, N = 8	**Clinical S3 – no, N = 12**	
PCWP	19 (10.5 - 23)	9.5 (7 - 16)	0.130
PA pressure - mean	26.5 (18.5 – 33.5)	16.5 (13.5 - 25)	0.140
RA pressure	5 (3 - 7)	3 (2 - 10)	0.850
	Pulmonary Rales – yes, N = 6	**Pulmonary Rales – no, N = 14**	
PCWP	18 (10 - 24)	9.5 (7 - 17)	0.160
PA pressure - mean	23.5 (18 - 43)	16.5 (13 - 26)	0.120
RA pressure	7 (3 - 14)	3.5 (2 - 6)	0.140
	Peripheral Oedema – yes, N = 4	**Peripheral Oedema – no, N = 16**	
PCWP	22 (17.5 - 35)	9.5 (7 - 16.5)	0.030
PA pressure - mean	34.5 (25 - 49.5)	16.5 (13.5 - 24.5)	0.020
RA pressure	12.5 (9 - 18.5)	3 (2 - 6)	0.007

10 of 20 patients (50%) had a JVP visible over 4 cm. When analysed in these 10 people, in order of magnitude, JVP was highly correlated with right atrial pressure (r_{sp} = 0.76, p = 0.015), mean PA pressure (r_{sp} = 0.66, p = 0.043) and PCWP (r_{sp} 0.64, p = 0.048) (**Figure 5-6**).

Figure 5-6 Spearman correlations between JVP on examination and RHC measures



5.4.5.8 Correlation between clinical symptoms and invasive measures on RHC

9 of 20 (45%) people self-reported orthopnoea. People with orthopnoea, compared to those without orthopnoea, did not have higher PCWP, mean PA pressure or right atrial pressure. The majority [15 of 20 (75%)] of people reported frequent dyspnoea as graded on the EVEREST congestion scale. There was a numerical pattern of higher PCWP, mean PA pressure and right atrial pressure in patients with incrementally greater degrees of dyspnoea that did not reach statistical significance. When patients were categorized according to NYHA class, 7 (35%) had class II symptoms, 12 (60%) were in class III and 1 person was class IV (5%). The

median values of PCWP, mean PA pressure and right atrial pressure were each greater across higher NYHA class but reached statistical significance for right atrial pressure only (p = 0.042). 13 (65%) of the cohort reported bendopnoea. Again, there was a numerical pattern of higher intra-cardiopulmonary pressures in these patients compared with people who did not have bendopnoea which was not statistically significant **(Table 5-10**).

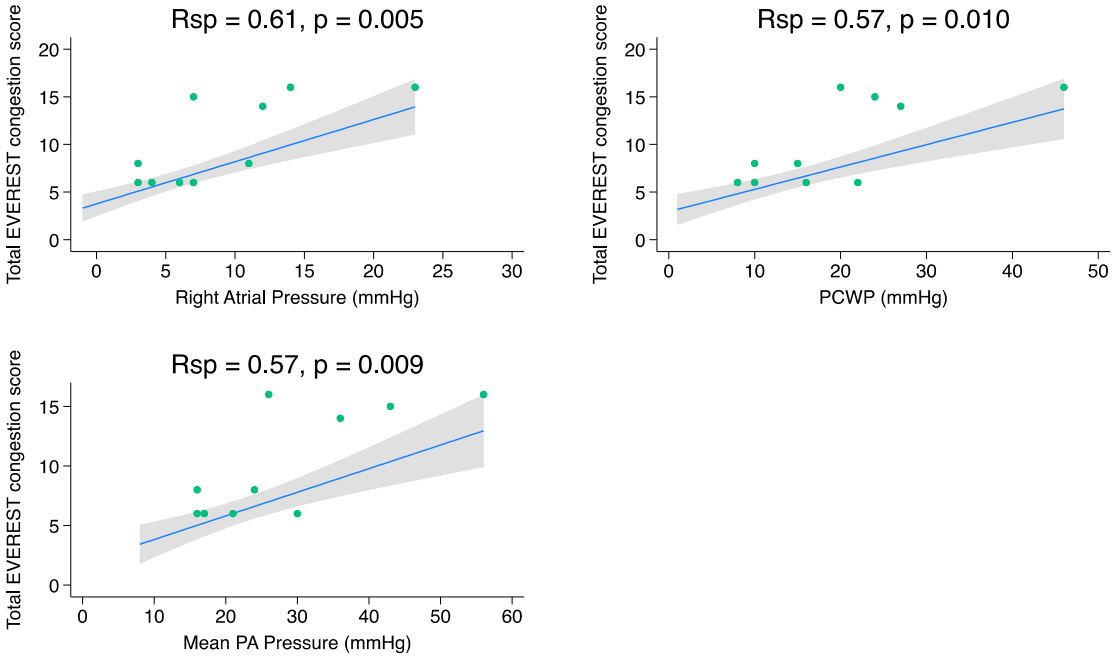
Table 5-9 RHC values according to presence or absence of clinical symptoms of congestion

RHC	Clinical Parameter		p =
	Orthopnoea – yes, N = 9	**Orthopnoea – No, N = 11**	
PCWP	9 (7 - 22)	13 (8 - 20)	0.730
PA pressure - mean	18 (14 - 30)	21 (16 - 26)	0.850
RA pressure	4 (2 - 6)	4 (0 - 11)	1.000
	Bendopnoea – yes, N = 13	**Bendopnoea – No, N = 7**	
PCWP	13 (8 - 20)	10 (3 - 22)	0.530
PA pressure - mean	21 (16 - 26)	17 (11 - 31)	0.630
RA pressure	6 (2 - 9)	3 (2 - 7)	0.520

EVEREST – Dyspnoea grade	**0, N = 1**	**1, N = 3**	**2, N = 15**	**3, N = 1**	**p =**
PCWP	3 (3 - 3)	8 (1 - 13)	15 (8 - 22)	46 (46 - 46)	0.088
Mean PA Pressure	11 (11 - 11)	16 (8 - 23)	21 (15 - 30)	56 (56 - 56)	0.120
Right Atrial Pressure	0 (0 - 0)	2 (-1 - 4)	6 (3 - 9)	23 (23 - 23)	0.073
NYHA class	**1, N = 0**	**2, N = 7**	**3, N = 12**	**4, N = 1**	**p =**
PCWP	-	8 (3 - 22)	12.5 (8.5 – 18.5)	46 (46 - 46)	0.180
Mean PA Pressure	-	16 (11 - 31)	19.5 (15.5 - 26)	56 (56 - 56)	0.220
Right Atrial Pressure	-	2 (0 - 4)	6 (3 – 10)	23 (23 - 23)	0.042

The total EVEREST congestion score was correlated with right atrial pressure (r_{sp} = 0.61, p = 0.005), PCWP (r_{sp} = 0.57, p = 0.010) and mean PA pressure (r_{sp} = 0.57, p = 0.009) (**Figure 5-7**).

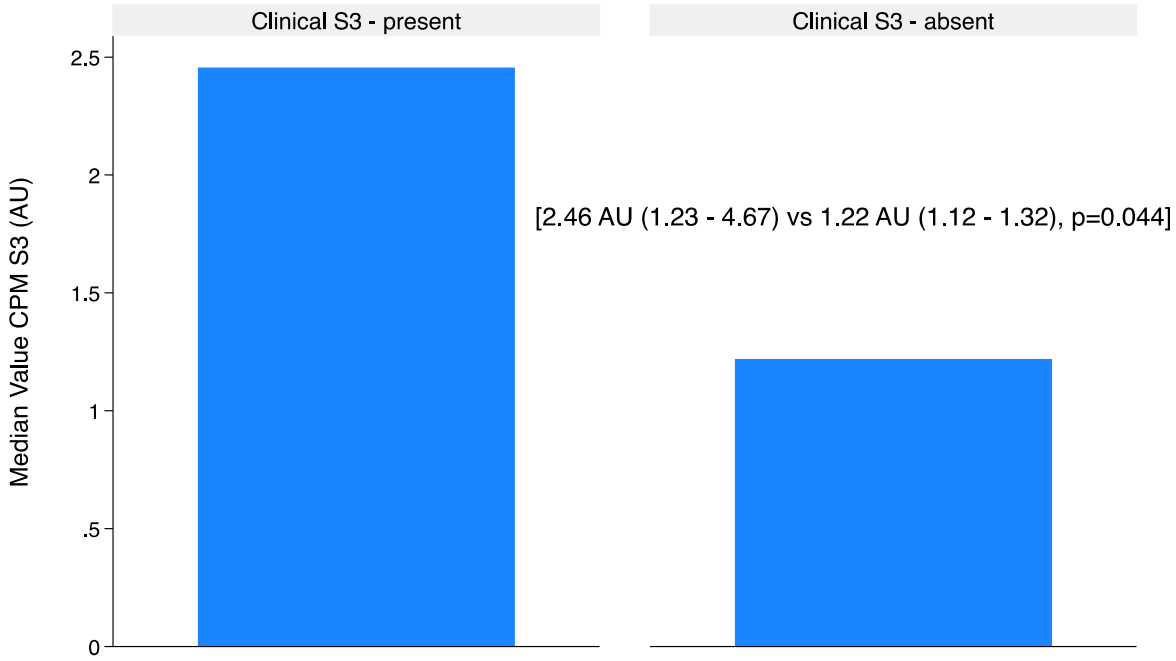
Figure 5-7 Spearman correlations of the total EVEREST congestion score and RHC measures



5.4.5.9 Correlation between CPM device measurements and clinical examination

Patients who had a S3 on examination also had a higher device S3 than those who did not have a S3 detected clinically [2.46 AU (1.23 - 4.67) vs 1.22 AU (1.12 - 1.32), p=0.044) (**Figure 5-8**).

Figure 5-8 CPM device S3 values according to the presence or absence of clinical S3



There was no difference between CPM device thoracic impedance [89.5 ohms (49.8 – 107.8) versus 70.8 ohms (62.6 – 125.2), p = 0.640] or CPM device tidal volume [1.1 ohms (0.5 – 1.7) versus 0.8 ohms (0.5 – 1.1), p = 0.560] in patients who did or did not have an audible S3 on examination.

People who had audible pulmonary rales on examination compared with those without rales, had no difference in CPM device thoracic impedance [79.4 ohms (55.4 – 116.4) versus 77.7 ohms (64.7 – 117.6), p = 0.620], CPM S3 [1.3 AU (1.1 – 1.9) versus 1.3 AU (1.1 – 1.9), p =

0.930] or CPM device tidal volume [0.9 ohms (0.5 – 1.3) versus 0.8 ohms (0.5 – 1.2), p = 0.900].

There was no difference between people who had peripheral oedema compared with people who did not in CPM S3 [1.6 AU (1.3 – 2.5) versus 1.2 AU (1.1 – 1.7), p = 0.240], CPM thoracic impedance [60.9 ohms (46.1 – 82.3) versus 89.5 ohms (62.6 – 118.7), p = 0.190] or CPM device tidal volume [1.1 ohms (0.8 – 1.5) versus 0.8 ohms (0.5 – 1.2), p = 0.300].

CPM device S3 (r_{sp} = 0.56, p = 0.096), CPM device thoracic impedance (r_{sp} = -0.38, p = 0.276) or CPM device tidal volume (r_{sp} = 0.25, p = 0.475) were not significantly correlated with JVP on examination.

5.4.5.10 Correlation between CPM device measurements and clinical symptoms

There was a general trend towards increasing values in CPM device S3, thoracic impedance and tidal volume across higher grades of the EVEREST dyspnoea scale that did not reach statistical significance. A similar general trend was observed across NYHA functional classes (**Table 5-11**).

Table 5-10 CPM device values according to the severity of clinical symptoms

EVEREST – Dyspnoea grade	**0, N = 1**	**1, N = 3**	**2, N = 15**	**3, N = 1**	**p =**
CPM S3 (AU)	1.1 (1.1 – 1.1)	1.3 (1.2 – 5.6)	1.2 (1.1 – 1.9)	1.9 (1.9 – 1.9)	0.590
CPM Thoracic Impedance (ohms)	33.1 (33.1 - 33.1)	75.2 (53.4 – 117.6)	80.1 (60.5 – 119.8)	98.2 (98.2 – 98.2)	0.420
CPM Tidal Volume (ohms)	0.8 (0.8 – 0.8)	1.0 (0.5 – 1.4)	0.8 (0.5 – 1.2)	1.6 (1.6 – 1.6)	0.570
NYHA class	**1, N = 0**	**2, N = 7**	**3, N = 12**	**4, N = 1**	**p =**
CPM S3 (AU)	-	1.4 (1.2 – 5.6)	1.2 (1.1 – 1.3)	1.9 (1.9 – 1.9)	0.130
CPM Thoracic Impedance (ohms)	-	53.4 (36.7 – 117.6)	89.5 (65.1 – 118.1)	98.2 (98.2 – 98.2)	0.340
CPM Tidal Volume (ohms)	-	1.0 (0.6 – 1.4)	0.7 (0.4 – 1.1)	1.6 (1.6 – 1.6)	0.150

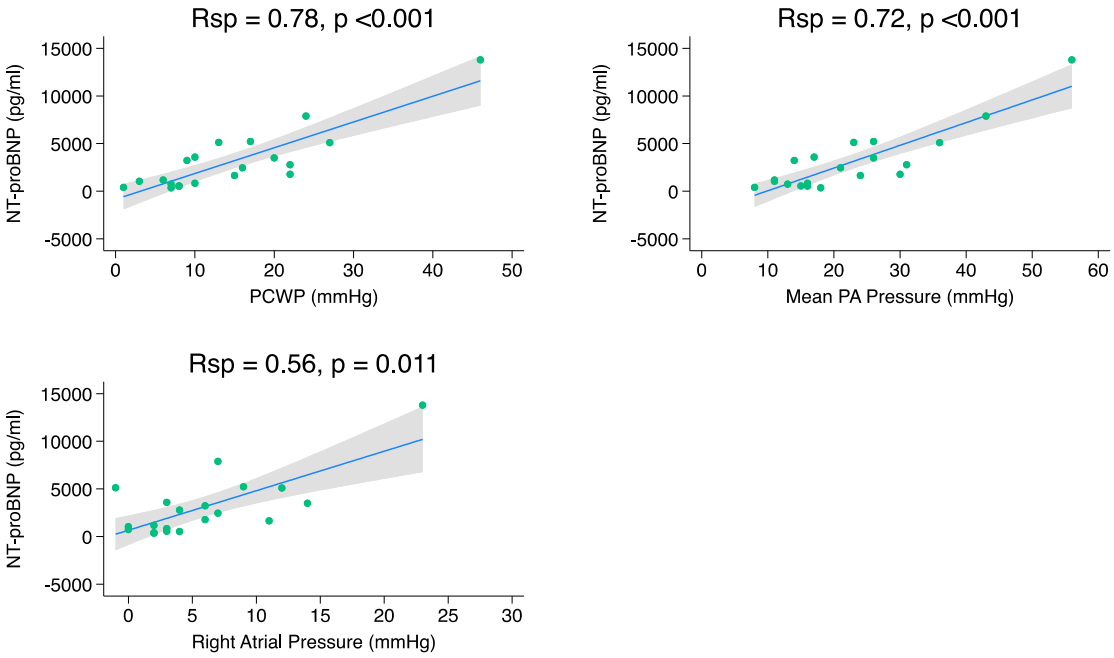
Among patients who self-reported bendopnoea, CPM device thoracic impedance was higher compared with people without bendopnoea [99.3 ohms (80.1 – 119.8) versus 64.7 ohms (36.7 – 66.4), p = 0.008]. There was no difference between these two groups in CPM device tidal volume [0.6 ohms (0.5 – 1.0) versus 1.2 ohms (0.8 – 1.3), p = 0.100] or CPM S3 [1.2 AU (1.1 – 1.9) versus 1.3 AU (1.1 – 3.0), p = 0.660]. Similarly, CPM device S3 [1.0 AU (0.5 – 1.6) versus 0.8 AU (0.5 – 1.2), p = 0.490], thoracic impedance [80.1 ohms (65.5 – 99.3) versus

66.4 ohms (53.4 – 117.6), p = 0.570] and tidal volume [1.0 ohms (0.5 – 1.6) versus 0.8 (0.5 – 1.2), p = 0.490] were not different respectively between patients who self-reported orthopnoea compared with those who did not. Total EVEREST congestion score did not correlate with CPM device S3 (r_{sp} = 0.05, p = 0.848), thoracic impedance (r_{sp} = 0.005, p = 0.982) or tidal volume (r_{sp} = 0.06, p = 0.794).

5.4.5.11 Correlation between congestion biomarkers and invasive measures on RHC

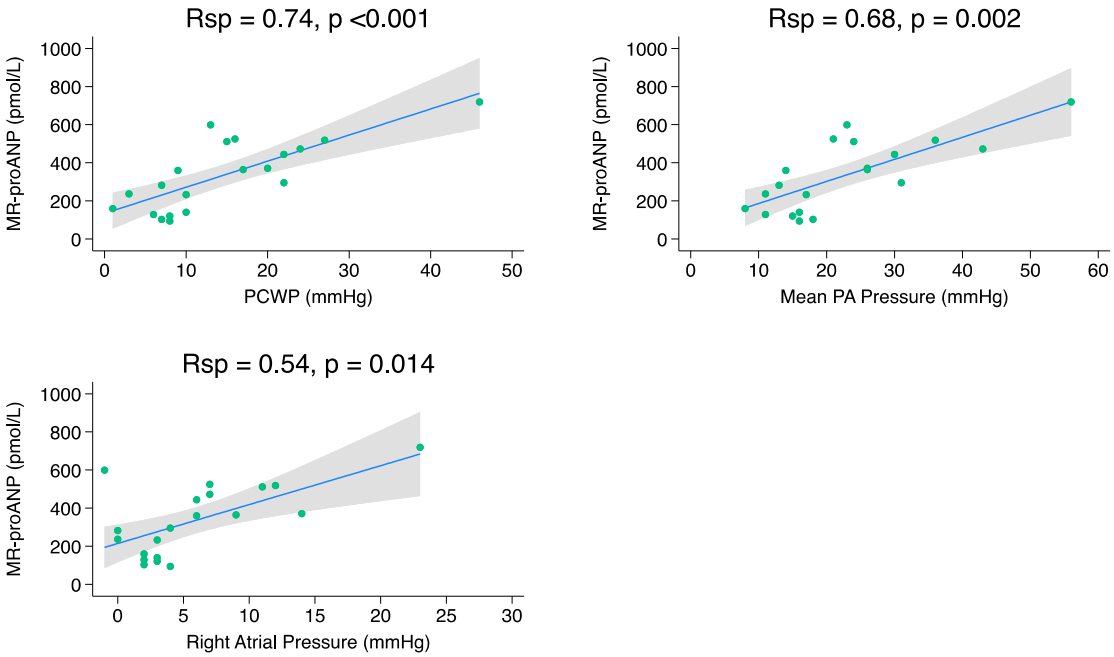
The median NT-proBNP was 2116 pg/ml (784 - 4341). All 20 patients had NT-proBNP measured. NT-proBNP was strongly correlated with PCWP (r_{sp} = 0.78, p <0.001), mean PA pressure (r_{sp} = 0.72, p <0.001) and more modestly with right atrial pressure (r_{sp} = 0.56, p = 0.011) on RHC.

Figure 5-9 Scatterplots of correlations between NT-proBNP and RHC measures



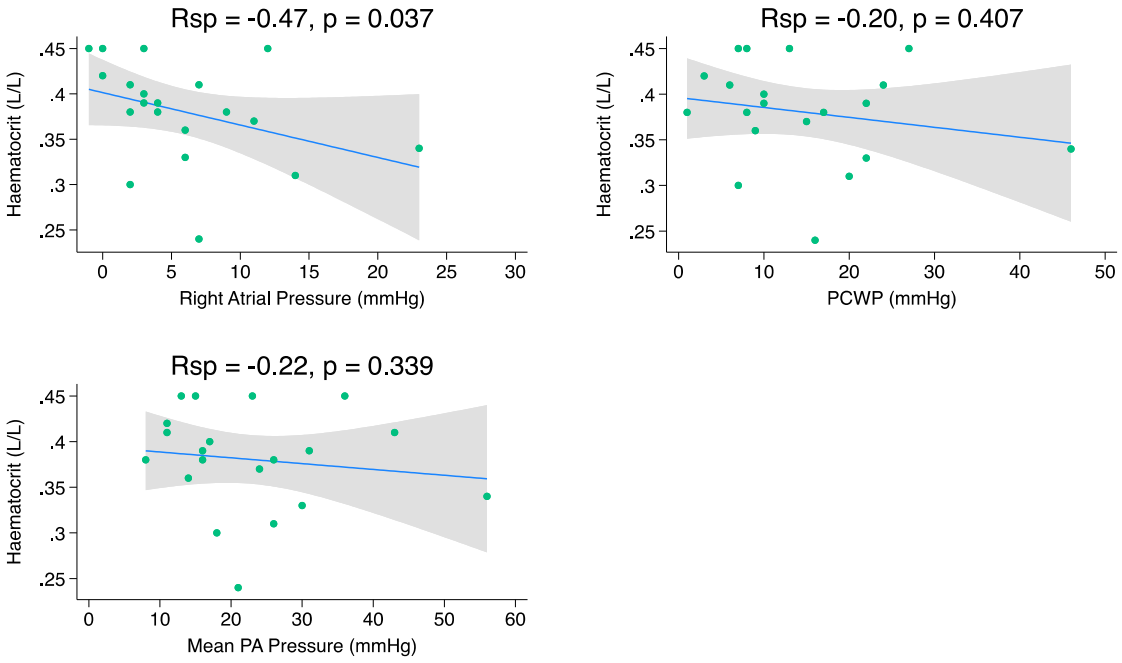
The median MR-proANP was 327 pmol/L (150 - 491). All 20 patients had MR-proANP measured. MR-proANP was strongly correlated with PCWP (r_{sp} = 0.74, p <0.001), mean PA pressure (r_{sp} = 0.68, p = 0.002) and again more modestly with right atrial pressure (r_{sp} = 0.54, p = 0.014) on RHC.

Figure 5-10 Scatterplots of correlations between MR-proANP and RHC measures



The median haematocrit was 0.39 L/L (0.35 – 0.42). All 20 patients had haematocrit measured. Haematocrit correlated significantly with right atrial pressure (r_{sp} = -0.47, p = 0.037) but not with PCWP (r_{sp} = -0.20, p = 0.407), mean PA pressure (r_{sp} = -0.22, p = 0.339) and on RHC.

Figure 5-11 Scatterplots of correlations between haematocrit and RHC measures



5.4.5.12 Correlation between CPM device measurements and congestion biomarkers

NT-proBNP was not significantly correlated with CPM device S3 (r_{sp} = 0.38, p = 0.094), thoracic impedance (r_{sp} = -0.01, p = 0.665) or tidal volume (r_{sp} = 0.21, p = 0.373) (**Figure 5-12**). MR-proANP was significantly correlated with CPM device S3 (r_{sp} = 0.47, p = 0.040) but not thoracic impedance (r_{sp} = -0.08, p = 0.722) or tidal volume (r_{sp} = 0.13, p = 0.582) (**Figure 5-13**). Haematocrit was not correlated with CPM device S3 (r_{sp} = 0.30, p = 0.195), thoracic impedance (r_{sp} = -0.14, p = 0.560) or tidal volume (r_{sp} = 0.17, p = 0.476) (**Figure 5-14**).

Figure 5-12 Scatterplots of correlations between CPM device measures and NT-proBNP

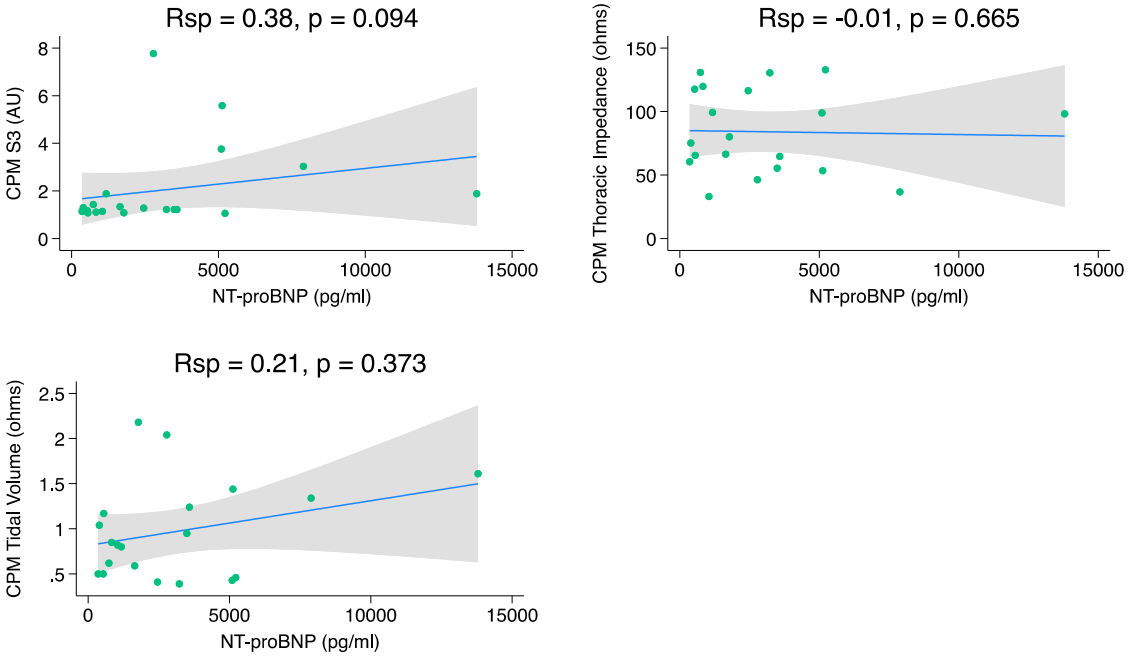


Figure 5-13 Scatterplots of correlations between CPM device measures and MR-proANP

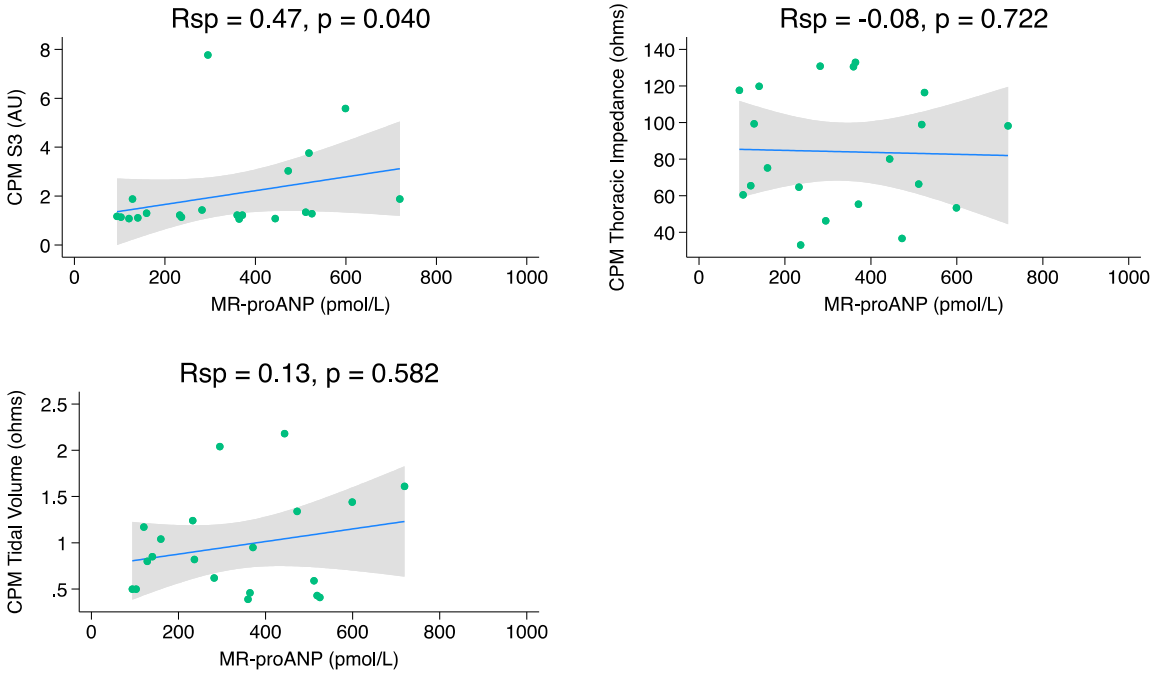
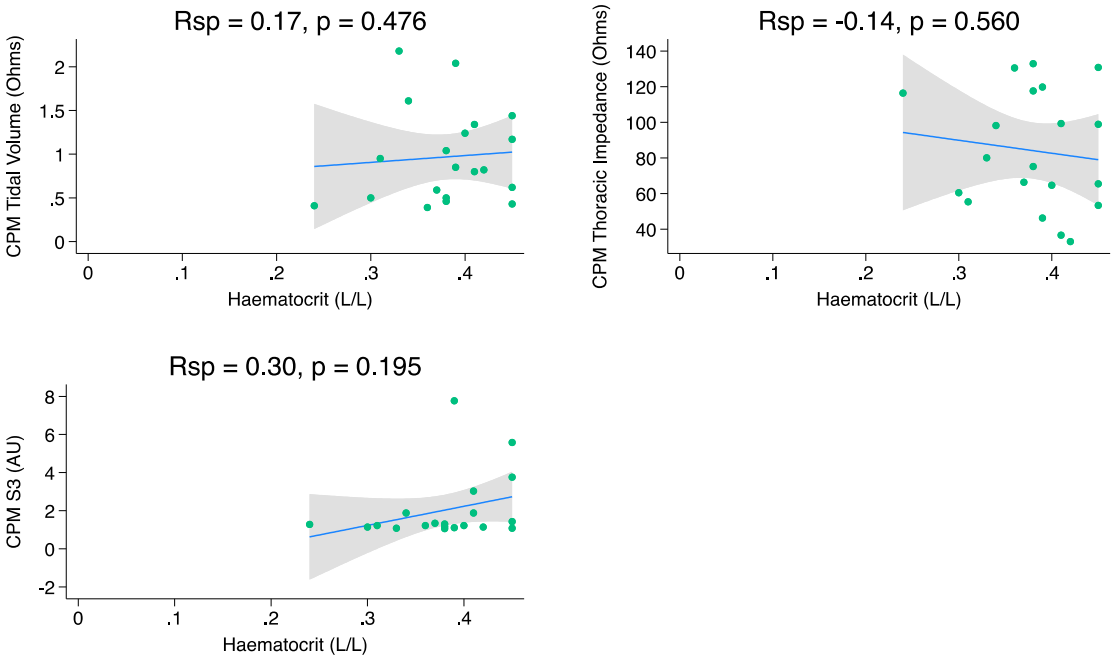


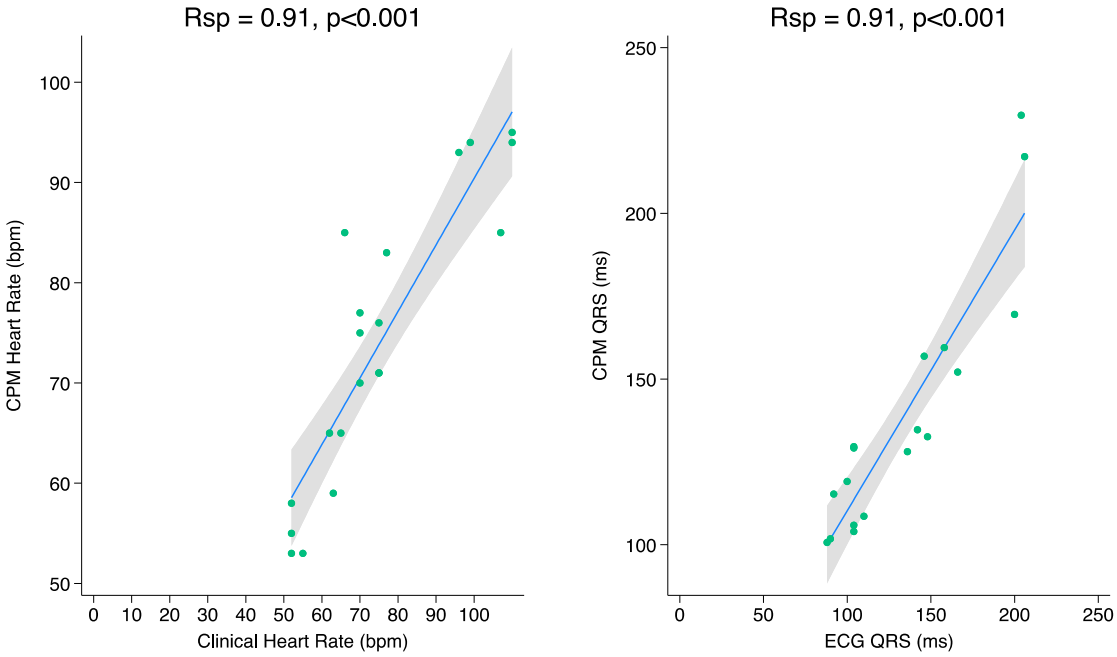
Figure 5-14 Scatterplots of correlations between CPM device measures and haematocrit



5.4.5.13 Correlation between CPM device measurements and clinical heart rate and ECG measures

The median heart rate on examination was 70 (62.5 – 86.5) beats per minute (bpm). All 20 patients had heart rate recorded. Clinical heart rate was highly correlated with heart rate as measured by the CPM device (r_{sp} = 0.91, p<0.001). A twelve lead ECG was performed in 18 of 20 (90%) patients as part of standard care. The median QRS duration on 12-lead surface ECG was 123ms (104 - 158). QRS duration on surface ECG was highly correlated with QRS duration measured by the CPM device (r_{sp} = 0.91, p<0.001) (**Figure 5-15**).

Figure 5-15 Scatterplots of correlations between CPM device heart rate and QRS duration and clinical heart rate and ECG QRS duration



On clinical examination, an irregular pulse was found in 6 patients and the CPM device Rhythm algorithm identified 4 patients with an irregular rhythm (Kappa = 0.47, p = 0.014). 4 of 18 patients who had an ECG on the study day were in atrial fibrillation. The CPM device heart rhythm algorithm detected atrial fibrillation in 3 of these 4 people. The fourth person was in atrial fibrillation but had a regularly-paced rhythm following an AV-node ablation and therefore did not meet the Rhythm parameter criteria for a positive finding which requires both absence of p waves and an unstable R-R interval. The Rhythm parameter reported no atrial fibrillation in all 14 of the people who were not in atrial fibrillation on ECG (Kappa = 0.82, p = <0.001).

5.4.6 Adverse Events

There were no device related adverse events in this study cohort, including no evidence of device-device interaction in any patients with an implanted cardiac device.

5.4.7 Device Deficiencies

3 device deficiencies occurred during this study as detailed below. No device deficiency resulted in loss of study data (**Table 5-12**).

Table 5-11 Description of device deficiencies

Date	Device ID	Patient ID	Type of Incident	When deficiency was identified	Action taken
10/03/2022	ADI11640-2	01009	Device malfunction – auscultation waveform change	During use	No action required – 2 previous valid readings. Report filed by Analog Devices Inc concluding external / environmental noise interference. Device returned as ADI11640-3.
17/03/2022	ADI11604-3	01014	Device malfunction – adhesive peeled	During use	Adhesive replaced
03/04/2022	ADI11640-3	01009	Device malfunction – adhesive peeled	During use	Adhesive replaced

5.5 Discussion

Compared with cohorts B and C in CONGEST-HF, who were specifically recruited because they were actively experiencing congestion, in this study I enrolled patients with advanced HF undergoing RHC as part of an evaluation for transplantation or mechanical circulatory support. The anticipation at study design was that these would be highly congested patients but volume status (or treatment to relieve excess fluid) was not a pre-requisite for participation. Given the cohort was comprised of both outpatients and acutely decompensated inpatients, there was a broad variety in haemodynamic states demonstrated by the PCWP values ranging from 1 mmHg (haemodynamically dry) to 46 mmHg (severely congested). Despite being clinically considered to be in an advanced stage of disease, two patients were not on loop diuretics when assessed indicating that their treating physicians did not feel they were chronically congested and on average the cohort had haemodynamic pressures that were within normal range.

Nonetheless, 95% of the cohort reported breathlessness, most of whom said this was on a frequent basis. The apparent discordance between the cardinal symptom of HF and the obtained cardiopulmonary values could be attributable to elevations in filling pressures on exertion as has been well-described[168,169]. Equally, there is the potential limitation of a single time providing only a cross sectional data point that does not reflect fluctuations in congestion that occur depending on fluid intake, medication changes or compliance and dynamic physiological conditions including changes in heart rhythm or blood pressure in vulnerable cohorts such as this one.

The CPM device S3 did not correlate with PCWP at this single-time point. There are several factors to consider to try and explain why the correlation was so weak and statistically

insignificant. Firstly, the variation in the two parameters was different with a much smaller dynamic range in CPM device S3 compared with PCWP that may have affected the strength of the correlation. Secondly, S3, often considered a physical marker of left ventricular filling pressures, has mixed performance when correlated with invasive measures obtained on RHC and differs depending on the population studied[225,226]. Studies previously reporting on the relationship between clinical S3 and PCWP in patients with HF were conducted in people who had been admitted with decompensation of HF and the mean PCWP values were considerably higher and the sample sizes larger than in the current study. In this study, while there was a numerical difference, PCWP was not statistically different between people who had or did not have a clinical S3 on examination. Thirdly, a clinical S3 can also be auscultated when left ventricular filling occurs into a non-compliant ventricle, regardless of PCWP. Irrespective of filling pressures at the time of RHC, this study cohort had echocardiographic evidence of significant diastolic dysfunction, supported by findings of a substantially reduced mitral valve inflow deceleration time, an elevated LAVI and E/e', conditions that could have increased the likelihood of auscultating a S3 and for the device to detect higher S3 energy in these patients. The existence of a greater degree of left ventricular remodelling and wall stress, in spite of normal range filling pressures at the time of RHC, was supported by the raised median natriuretic peptides (NT-proBNP and MR-proANP) in this cohort. CPM device S3 also correlated strongly with specific measures of left ventricular performance in this cohort and may act as a marker of severely impaired systolic function. While inter-rater variability exists when detecting a S3 on auscultation, with reported levels of agreement between kappa = 0.18 and kappa = 0.60[225,227], it was not possible to compare my examination findings against those of another investigator. However, it was notable that

people who had a clinical S3 also had a device S3 value two-fold higher than patients who did not have a S3 [2.46 AU (1.23 - 4.67) vs 1.22 AU (1.12 - 1.32), p=0.044).

Overall, CPM device parameters correlated poorly with invasive haemodynamic across the range of measures obtained. Put in the context of other remote monitoring devices, particularly implanted sensors, the ability of this wearable device to estimate filling pressures appears comparatively weaker. However, both the Chronicle and CardioMEMS devices were specifically designed to measure pressure and while they did so effectively with near exact correlation with RHC measures, one limitation of such targeted methods of monitoring is that pressure is not always commensurate with volume status despite conventional thinking that both conditions are entirely synonymous with one another[56,281]. A complex interplay between the unstressed and stressed blood volumes, physiological rather than anatomical compartments which I described in the Introduction, can result in states of high pressure but normal volume or low/normal pressure despite an expanded total body volume. Studies correlating haemodynamic pressures, obtained from implanted sensors, and total body volume measured by radio-labelled tracers have demonstrated a discordance between these measures. In one study, estimated PA diastolic pressure and total blood volume were poorly correlated ($r = 0.24$, $p = 0.330$) and only 6 of 18 (33.3%) patients had concordant trends in both parameters on serial measures. Another study of 20 patients found no correlation between PA diastolic pressures on CardioMEMS and total blood volume ($r_{sp} = 0.002$) or plasma volume ($r_{sp} = 0.001$) and using an experimental simulation model reported an increased but still weak correlation between pulmonary pressure and simulated stressed blood volume ($r_{sp} = 0.24$)[285]. While proprietary differences between devices and different study cohorts limits any direct comparison between the effectiveness of individual wearable devices to correlate with filling pressures, it is noteworthy that in the ESCAPE trial

bioimpedance sub-study of 170 patients there was no correlation between bioimpedance and PCWP when analysing parameters obtained at discharge when patients had been treated to achieve a PCWP <15mmHg (r = -0.01)[286]. Similarly in CONGEST-HF, CPM device thoracic impedance did not correlate with PCWP or pulmonary pressures but instead demonstrated an inverse correlation with LUS B-lines (r = -0.57, p = 0.010), a marker of congestion that in this cohort reflected haemodynamic pressure (r_{sp} = 0.61, p = 0.005 for correlation with PCWP) but also reliably estimated tissue and extravascular fluid volume as well in other studies[108]. LUS B-lines and spirometry tidal volume were also modestly correlated with CPM device tidal volume. CPM thoracic impedance or tidal volume were not correlated other clinical estimates of pulmonary function such as dyspnoea although discrimination between groups may have been difficult to establish as dyspnoea was present in nearly all patients.

Among the 18 of 20 patients who had an ECG performed as part of standard care on the day of the study, the CPM device showed strong correlation with both ECG heart rate and notably the ability to accurately discriminate between potential atrial fibrillation and sinus rhythm using the device Rhythm parameter. No patient in sinus rhythm was given a false positive Rhythm result. 1 person who was in atrial fibrillation was not given a positive Rhythm result. However, as described, this patient had an uncommon reason for the false negative, in that their underlying rhythm was atrial fibrillation but they were paced a regular R-R intervals due to a previous AV nodal ablation and therefore did not meet the programmed criteria for a Rhythm alert. This clinical circumstance of regularised atrial fibrillation is uncommon in the general HF population and represents a very specific limitation of the Rhythm screening parameter. However, based on the agreement achieved

with the baseline 12-lead ECG, the Rhythm detection algorithm otherwise performed strongly.

5.6 Limitations

I did not obtain both spirometry measurements at the same time because motion artefact would interfere with the CPM device readings. The patients were assessed at a single time-point and serial data on a sufficient number of people would have been desirable. However, outpatient RHCs were only repeated on a 6 monthly basis and inpatients often progressed to higher forms of support (eg intra-aortic balloon pump, Impella) which meant it would not be possible to perform serial device readings.

5.7 Conclusions

In this cohort of patients with advanced HF but overall normal haemodynamics, the CPM wearable device parameters did not correlate with intra-cardiopulmonary filling pressures. However, the device parameters did show relationships with LUS B-lines, a marker of broader systemic congestion, and in the case of device S3 there were relationships found with clinically auscultated S3, left ventricular remodelling (MR-proANP) and left ventricular performance (LVEF, LV GLS, LVOT VTI). The CPM device Rhythm parameter was highly effective at identifying patients with atrial fibrillation and ruling atrial fibrillation out in those patients in sinus rhythm and is a potentially valuable measure in the multi-parametric monitoring of patients at-risk of atrial arrhythmias as well as congestion.

6. CHAPTER SIX. A study of the non-invasive CardioPulmonary Management (CPM) device in patients with end-stage renal disease who were established on dialysis

6.1 Introduction

Similarly to patients with HF, people with end-stage renal disease who are haemodialysis dependent are prone to volume overload and have excess fluid removed at regular intervals while receiving haemodialysis. Sharing common risk factors such as hypertension and diabetes, cardiovascular disease is highly prevalent in people with renal disease and is the most common cause of death in this population[287,288]. HF is diagnosed in up to 50% of people receiving chronic haemodialysis and is associated with a poor prognosis compared with people on dialysis without HF[289,290]. Patients on dialysis exhibit congestion in a similar manner to people with HF, with pulmonary, abdominal and peripheral distribution of fluid accumulation. Differences in LUS, echocardiography and biomarkers including haematocrit have been examined in patients before and after dialysis in previous studies and changes in these measures have been reported following volume removal [105,291-294].

The volume of fluid removed by dialysis is often clinically important and readily quantifiable, making this cohort one which was well-suited to investigate whether the CPM device was able to detect rapid or large changes in volume status. In this study of patients undergoing a single dialysis session, I examined whether the CPM device measures correlated with the volume of fluid removed as well as serial measures of LUS, spirometry, clinical signs and symptoms, echocardiography, biomarkers of congestion and ECG parameters. Relations between change in these measures, before and after dialysis, were also examined.

6.2 Methods

Patients were recruited into this study on Ward 4D at the QEUH when they were receiving inpatient medical care. Inclusion and exclusion criteria and study objectives for this cohort (Cohort B) were detailed in **Chapter 4**.

6.2.1 Study procedures

As per Cohort A, CPM device readings and data transfer, echocardiography, LUS, spirometry, blood phlebotomy and analysis were all carried out in accordance with the CONGEST-HF study standard operating procedures (**Appendix**). A study assessment (visit 1) was performed immediately before dialysis and volume removal began. The last assessments for visit 1 were LUS and then the CPM device readings. Blood was taken when the patient was connected to the dialysis circuit. The patient was then immediately started on dialysis when the device readings were completed. Once dialysis was finished the same series of study measurements were taken, starting in order with blood phlebotomy while still on the circuit, the CPM device reading and then LUS. A clinical history and examination and observations were performed before and after dialysis. Haemodialysis was performed using a Nikkiso DBB-EXA haemodialysis circuit pre-programmed to remove a target volume according to the patient's estimated requirements. The primary clinical team determined the volume to be removed and as per the inclusion criteria a minimum of 1.5L was required to be eligible for this study.

6.2.2 Statistical Analyses

Continuous variables were summarised using the mean and standard deviation (SD) or median with inter-quartile ranges (IQR) depending on the normality of the data. Categorical variables were summarised with frequencies and percentages. Individual-patient Spearman correlations were used to determine the correlations between device measurements and clinical parameters that were continuous variables. Scatterplots graphically represent the correlations. When analysed according to individual study visit, relations between continuous and categorical variables were analysed using Mann-Whitney-Wilcoxon tests or Kruskal-Wallis tests as appropriate. The Wilcoxon signed rank test was used to analyse the relationship between change in continuous variables measured before and after dialysis. McNemar's test was used to examine the relationship between change in categorical variables before and after dialysis. In addition, where a CPM reading represented the same quantity as a categorical variable, outcomes were compared using weighted kappa statistics. A p value <0.05 was considered statistically significant. Analyses were performed using STATA version 18 (College Station, Texas, USA).

6.3 Results

21 patients with end-stage renal disease and who were established on intermittent haemodialysis for a minimum of 90 days were recruited into the study between 26th November 2021 and 22nd July 2022. This cohort were pre-dominantly male with a mean age 60.1 ± 14.9 years. 5 of 21 (23.8%) patients had a history of HF of whom 3 were due to an ischaemic aetiology. In keeping with the expected prevalence of morbidity in patients with renal disease, the majority of people had at least one cardiovascular risk factor, most often hypertension (71.4%) followed by diabetes (28.6%) and a prior myocardial infarction

(19.1%). The median volume of fluid removed by haemodialysis was 1999 mls (1600 - 2000).

Baseline characteristics are described in **Table 6-1**.

Table 6-1 Baseline characteristics of people enrolled into Cohort B of the CONGEST-HF study

	Cohort B
N = (%)	21
Male sex (%)	15 (71.4)
Age (years)	60.1 ± 14.9
Race (%)	
White	19 (90.5)
Black	-
Asian	2 (9.5)
Other	-
BMI (kg/m^2)	25.4 ± 5.3
Medical History (%)	
Hypertension	15 (71.4)
Diabetes	6 (28.6)
AF on baseline ECG	5 (23.8)
History of any AF	6 (28.6)
MI	4 (19.0)
Stroke	2 (9.5)
COPD	1 (4.8)
LVEF (%)	48 ± 17
NYHA Class (%)	
I	4 (19.0)
II	5 (23.8)

III	9 (42.9)
IV	3 (14.3)
Symptoms/signs (%)	
Dyspnoea	16 (76.2)
Orthopnoea	8 (38.1)
PND	5 (23.8)
Fatigue	19 (90.5)
Bendopnoea	9 (42.9)
Peripheral oedema	6 (28.6)
Systolic BP (mmHg)	138 ± 34
Heart rate (bpm)	80 ±15
Respiratory rate (per min)	16 ± 0.5
Chest circumference (cm)	102 ± 13
Duration of HF	
<1 year	3 (14.3)
1 – 5 years	3 (14.3)
>5 years	1 (4.8)
Ischaemic aetiology for HF (%)	3 (14.3)
Prior HF Hospitalization (%)	1 (4.8)
HF Hospitalization within previous 6 months (%)	1 (4.8)
NT-proBNP (pg/ml)	43624 (4955 - 88720)
MR-proANP (pmol/L)	1251 (670 - 1857)

eGFR (mL/min/1.73m^2)	7 (5 - 10)
Haematocrit (L/L)	0.30 ± 0.03
ECG – sinus (%)	15 (71.4)
ECG – AF (%)	5 (23.8)
ECG – Paced rhythm (%)	1 (4.8)
Baseline treatment (%)	
Loop diuretic	5 (23.8)
Thiazide / Thiazide-like diuretic	0 (0.0)
ACE inhibitor or Angiotensin Receptor Blocker	5 (23.8)
Sacubitril / Valsartan	1 (4.8)
Beta-blocker	16 (76.2)
MRA	0 (0.0)
SGLT2 inhibitor	0 (0.0)
Digoxin	1 (4.8)
Any implanted device	1 (4.8)
ICD	0 (0.0)
CRT-D	0 (0.0)
CRT-P	0 (0.0)
Pacemaker	1 (4.8)
Loop recorder	0 (0.0)

ACE = angiotensin converting enzyme; AF = atrial fibrillation; BMI = body mass index; COPD = chronic obstructive pulmonary disease; CRT-D = cardiac resynchronization therapy-defibrillator; CRT-P = cardiac resynchronization therapy-pacemaker; ECG = electrocardiogram; eGFR = estimated glomerular filtration rate; HF = heart failure; ICD = implantable cardioverter defibrillator; LVEF = left ventricular ejection fraction; MI = myocardial infarction; MRA = mineralocorticoid receptor antagonist; MR-proANP = mid regional pro-atrial natriuretic peptide; NT-proBNP = n-terminal pro-B type natriuretic peptide; NYHA = New York Heart Association; PND = paroxysmal nocturnal dyspnoea; SGLT2 = sodium glucose co-transporter 2.

6.3.1 Change in CPM device measures after dialysis

Compared with before dialysis, CPM device thoracic impedance and tidal volume both increased when volume was removed by dialysis. There was no apparent difference in CPM device S3 measured before and after dialysis (**Table 6-2**).

Table 6-2 CPM device values before and after dialysis

CPM device parameter	Before Dialysis	After Dialysis	p =
Thoracic Impedance	40.0 (30.7 – 72.2)	48.5 (38.6 – 83.0)	0.001
S3	1.2 (1.1 – 1.6)	1.3 (1.1 – 2.1)	0.135
Tidal Volume	0.63 (0.35 – 0.74)	0.72 (0.44 – 0.88)	0.017

6.3.2 Primary analyses

6.3.2.1 Correlation of change in LUS B-lines and volume of fluid removed

All 21 patients had LUS performed before and after dialysis. At baseline, in order of magnitude, the median number of B-lines per zone was; zone 6 [11 (4 - 13)], zone 8 [10 (6 - 13)], zone 4 [7, (3 - 14)], zone 2 [7 (4 – 15)], zone 3 [5 (1 - 11)], zone 7 [5 (1 - 12)], zone 1 [3 (0 - 12)], zone 5 [2 (0 - 13)]. The median number of B-lines before dialysis was 58 (33 - 94) and after dialysis was 31 (15 - 67) (p value for difference <0.001). There was no evidence of inter-rater variability when a randomly selected cohort of 10% of LUS studies were examined by another investigator as part of a core-lab process. Change in B-lines was not correlated significantly with the volume of fluid removed by dialysis (r_{sp} = -0.29, p = 0.195).

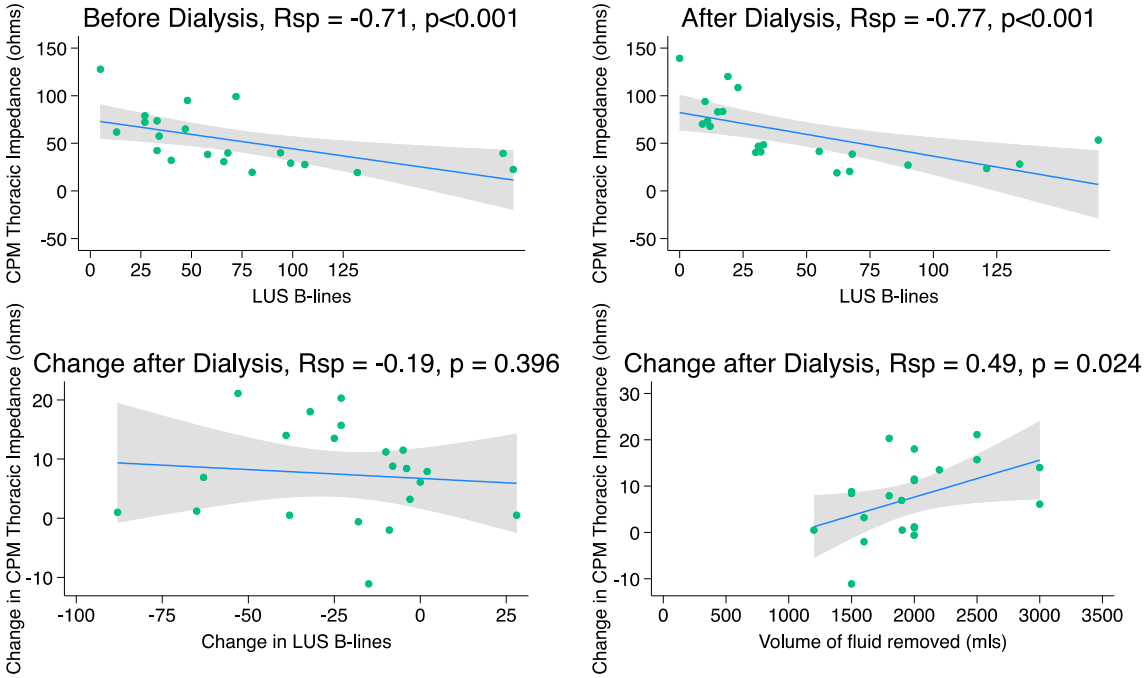
6.3.2.2 Correlation between CPM device thoracic impedance and LUS B-lines

CPM device thoracic impedance and B-lines on LUS were strongly correlated before (r_{sp} = -0.71, p<0.001) and after (r_{sp} = -0.77, p<0.001) dialysis. The correlation between change in device thoracic impedance and change in B-lines was weaker and did not reach statistical signficance (r_{sp} = -0.19, p = 0.396) (**Figure 6-1**).

6.3.2.3 Correlation of change in CPM device thoracic impedance and volume of fluid removed

When volume of fluid removed by dialysis was correlated with change in device thoracic impedance, the correlation coefficient was r_{sp} = 0.49, p=0.024 (**Figure 6-1**).

Figure 6-1 Scatterplots of CPM device thoracic impedance correlated with LUS B-lines



6.3.3 Secondary outcomes

6.3.3.1 Correlations between CPM device measures and volume of fluid removed by dialysis

Change in CPM S3 (r_{sp} = -0.24, p = 0.283) and change in CPM tidal volume (r_{sp} = 0.06, p = 0.810) after dialysis did not correlate significantly with fluid removed by dialysis.

6.3.3.2 Correlation between CPM device S3 and LUS B-line

CPM device S3 and LUS B-lines were significantly correlated with LUS B-lines before dialysis (r_{sp} = 0.48, p = 0.028). The strength of the correlation was weaker after dialysis (r_{sp} = 0.40, p = 0.075), and when change in both parameters were analysed (r_{sp} = 0.43, p = 0.055) was of borderline statistical significance.

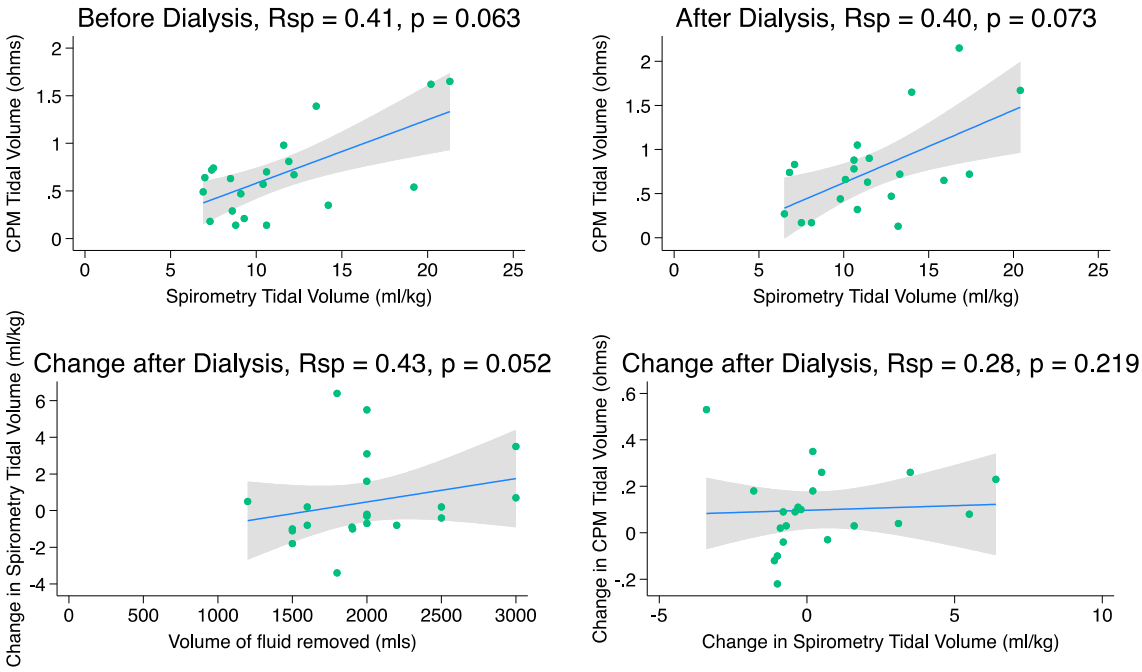
6.3.3.3 Correlation between CPM device tidal volume and LUS B-lines

CPM device tidal volume and B-lines were poorly correlated before (r_{sp} = 0.07, p = 0.778) and after (r_{sp} = 0.13, p = 0.562) dialysis and when change in both parameters was analysed (r_{sp} = 0.03, p = 0.889).

6.3.3.4 Correlation between CPM device tidal volume and tidal volume by spirometry

All 21 patients had tidal volume measured by bedside spirometry before and after dialysis. The median spirometry tidal volume before dialysis was 10.4 ml/kg (8.5 – 12.2) and after dialysis was 10.8 ml/kg (9.8 – 13.3) (p value for difference = 0.862). There was a modest correlation between spirometry tidal volume and volume of fluid removed by dialysis of borderline statistical significance (r_{sp} = 0.43, p = 0.052). Tidal volume by spirometry was not significantly correlated with CPM device tidal volume before (r_{sp} = 0.41, p = 0.063) or after dialysis (r_{sp} = 0.40, p = 0.073). Change in device tidal volume did not correlate significantly with change in spirometry tidal volume (r_{sp} = 0.28, p = 0.219).

Figure 6-2 Scatterplots of CPM device tidal volume correlated with spirometry tidal volume



6.3.3.5 Echocardiography

6.3.3.5.1 Change in echocardiographic measures before and after dialysis

Echocardiography was performed according to the study SOP in all 21 patients before and after dialysis. Median values (IQR) are reported for the measured echocardiographic parameters per study visit in **Table 6-3**. Missing values, accounting for poor echocardiographic windows or factors such as atrial fibrillation, are reported below **Table 6-3.** E/A ratio, LAVI, TR Vmax changed significantly between study visits. There were no differences observed in LV GLS, LVOT VTI, left ventricular ejection fraction, E/e' ratio, MV inflow deceleration time, IVC diameter, PVAT when measured before and after fluid was removed by dialysis.

Table 6-3 Echocardiographic values before and after dialysis and calculated change in values.

Echocardiographic Parameter	Before Dialysis	After Dialysis	Median Change after Dialysis	p =
TR Vmax (m/s)	2.5 (1.9 – 3.0)	2.3 (1.5 – 2.8)	-0.2 (-0.5 to -0.1)	0.003
LAVI (ml/m^2)	52.6 (36.2 – 75.2)	41.5 (35.1 – 61.7)	-4.2 (-16.5 to 1.7)	0.024
E/A ratio	1.0 (0.8 – 1.9)	1.0 (0.8 – 1.3)	-0.1 (-0.6 to 0.02)	0.030
LV GLS (%)	-10.2 (-14.3 to -8.6)	-10.2 (-14.9 to -7.1)	-0.1 (-2.0 to 1.4)	0.691
LVOT VTI (cm)	22.9 (18.2 – 30.5)	21.0 (15.5 – 27.2)	-1.2 (-3.8 to 0.3)	0.131
PVAT (ms)	100 (88 - 133)	109 (95 - 145)	5 (-10 to 20)	0.164
MV inflow Deceleration (ms)	218 (169 - 264)	191 (154 - 237)	-9 (-32 to 31)	0.768
LVEF (%)	55 (30 - 60)	53 (33 - 60)	0 (-2 to 2)	0.834
E/e' ratio	12.7 (10.6 - 16)	12.6 (10.0 – 15.0)	0 (-1.7 to 0)	0.161
IVC diameter (mm)	17.5 (11.5 - 24)	16 (13 - 21)	-2 (-6 to 1)	0.055

Missing data before dialysis: LV GLS, n = 4; LVOT VTI, n = 1; E/A ratio, n = 5; IVC diameter, n = 1; LAVI, n = 2. Missing data after dialysis: LV GLS, n = 6; E/A ratio, n = 5; IVC diameter, n = 2; LA volume, n = 2; Missing data for change variables: LV GLS, n = 6; LVOT VTI, n = 1; E/A ratio, n = 5; IVC diameter, n = 2; LAVI, n = 2.

6.3.3.5.2 Correlation of volume of fluid removed by dialysis and change in echocardiographic measures

Volume of fluid removed by dialysis was correlated with TR vmax (r_{sp} = -0.48, p = 0.031). No other calculated change in echocardiographic parameters correlated significantly with fluid removed (**Table 6-4**).

Table 6-4 Spearman correlations of change in echocardiographic measures and volume of fluid removed by dialysis

Parameter	Spearman Correlation	P Value
TR Vmax (m/s)	-0.48	0.031
LAVI (ml/m^2)	-0.009	0.971
E/A ratio	-0.07	0.789
LV GLS (%)	0.33	0.226
LVOT VTI (cm)	0.13	0.569
PVAT (ms)	0.11	0.633
MV inflow Deceleration (ms)	0.23	0.318
LVEF (%)	-0.24	0.294
E/e' ratio	-0.29	0.203
IVC diameter (mm)	-0.01	0.977

6.3.3.5.3 Correlations between CPM device and echocardiography measures before dialysis

Of the correlations analysed between CPM device S3 and echocardiography measured before dialysis, only LAVI was significantly correlated with CPM device S3 (r_{sp} = 0.55, p = 0.017) (**Table 6-5**). LAVI (-0.56, p = 0.014) and PVAT (r_{sp} = 0.49, p = 0.026), but no other echocardiographic measures before dialysis, were correlated significantly with CPM device thoracic impedance. Only TR Vmax (r_{sp} = -0.44, p = 0.048) significantly correlated with CPM device tidal volume before dialysis (**Table 6-5**).

Table 6-5 Spearman correlations (rsp) of echocardiographic and CPM device parameters before dialysis

Parameter	CPM Device S3 r_{sp} =	p =	CPM Device Thoracic Impedance r_{sp} =	p =	CPM Device Tidal Volume r_{sp} =	p =
LAVI (ml/m^2)	0.55	0.017	-0.56	0.014	-0.21	0.418
PVAT (ms)	-0.29	0.120	0.49	0.026	0.11	0.635
LVEF (%)	-0.25	0.265	0.11	0.627	-0.18	0.421
TR Vmax (m/s)	0.21	0.360	-0.28	0.225	-0.44	0.048
MV inflow deceleration (ms)	-0.23	0.317	-0.01	0.968	-0.18	0.420
LVOT VTI (cm)	-0.19	0.418	-0.04	0.874	-0.06	0.797
E/A ratio	-0.15	0.582	-0.20	0.463	-0.23	0.388
E/e' ratio	-0.12	0.593	-0.04	0.848	-0.26	0.257
IVC diameter (mm)	-0.12	0.626	0.22	0.353	-0.27	0.242
LV GLS (%)	0.06	0.824	0.16	0.538	-0.21	0.418

6.3.3.5.4 Correlations between CPM device and echocardiography measures after dialysis

When echocardiographic and CPM device parameters measured after dialysis were analysed, both LV GLS (r_{sp} = 0.60, p = 0.021) and PVAT (r_{sp} = -0.44, p = 0.048) were correlated with CPM device S3 (**Table 6-6**). No other echocardiographic parameters were correlated with device S3. The echocardiographic parameters that correlated significantly with CPM device thoracic impedance were TR Vmax (r_{sp} = -0.45, p = 0.042), LAVI (-0.49, p = 0.035) and PVAT (r_{sp} = 0.71, p <0.001). No echocardiographic parameters were significantly correlated with CPM device tidal volume after dialysis (**Table 6-6**).

Table 6-6 Spearman correlations (rsp) of echocardiographic and CPM device parameters after dialysis

Parameter	CPM Device S3 r_{sp} =	p =	CPM Device Thoracic Impedance r_{sp} =	p =	CPM Device Tidal Volume r_{sp} =	p =
LAVI (ml/m^2)	0.28	0.245	-0.49	0.035	-0.08	0.740
PVAT (ms)	-0.44	0.048	0.71	<0.001	-0.05	0.836
LVEF (%)	-0.14	0.554	0.002	0.993	-0.24	0.295
TR Vmax (m/s)	0.19	0.407	-0.45	0.042	-0.18	0.423
MV inflow deceleration (ms)	-0.42	0.057	0.21	0.354	-0.11	0.645
LVOT VTI (cm)	-0.21	0.348	-0.08	0.722	-0.27	0.239
E/A ratio	-0.34	0.198	0.34	0.192	-0.47	0.068
E/e' ratio	-0.21	0.353	-0.04	0.861	-0.32	0.156
IVC diameter (mm)	0.06	0.814	0.09	0.704	-0.03	0.911
LV GLS (%)	0.59	0.021	-0.34	0.219	0.14	0.603

6.3.3.5.5 Correlations between change in CPM device and change in echocardiography measures after dialysis

No significant correlations observed when change in CPM device S3, thoracic impedance or tidal volume were correlated with change in echocardiographic parameters after dialysis.

6.3.3.6 Clinical examination findings before and after dialysis

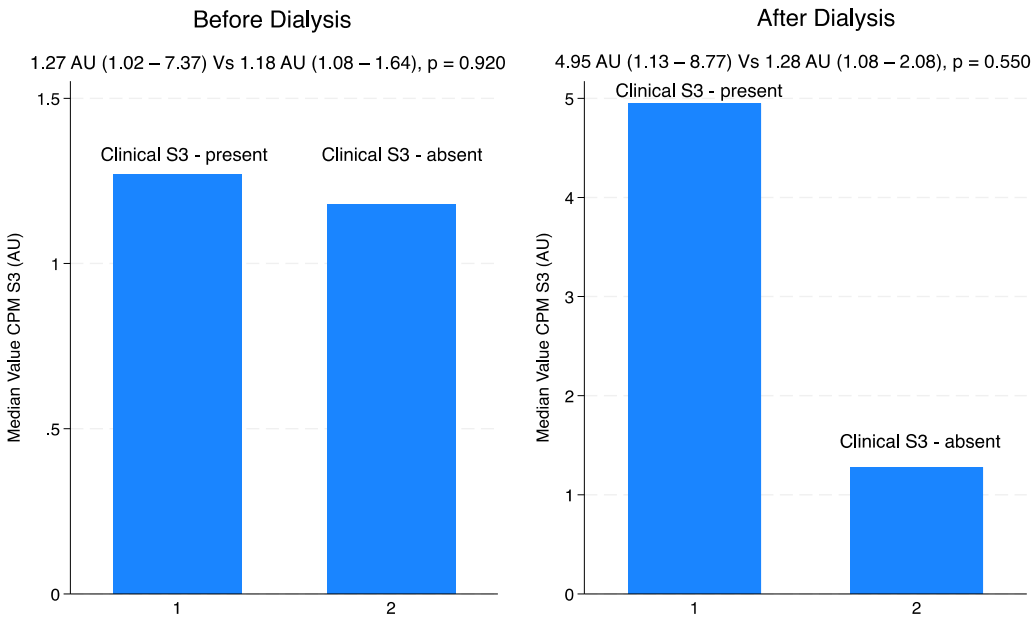
All 21 patients were examined before and after dialysis. 11 of 21 (52.4%) patients had an elevated JVP (>4cm) before dialysis. Among these 11 patients, the median measured JVP was 10 cm (8 - 15). Of the 11 patients with a visible JVP before dialysis, 7 of them (63.6%) had an elevated JVP after dialysis and 4 did not (p = 0.046), however the volume of fluid removed by dialysis did not differ between these two groups respectively [1904 (1600 - 3000) Vs 1900 (1650 - 2000), p = 0.630]. Among those people who had a visible JVP after dialysis, the median JVP elevation was 8 cm (6 - 15) (p value for difference with baseline = 0.101). Change in JVP elevation was poorly correlated with volume of fluid removed (r_{sp} = 0.18, p = 0.686).

3 of 21 (14.3%) patients had an audible clinical S3 on examination before dialysis. A clinical S3 was audible in 2 people after dialysis (p = 0.564). Pulmonary rales were audible in 15 of 21 people (71.4%) before dialysis and 13 patients (61.9%) afterwards (p = 0.414). Peripheral oedema was clinically evident in 6 of 21 (28.6%) people both before and after dialysis (p = 1.000).

6.3.3.7 Correlation between CPM device measures and clinical examination before and after dialysis

In people who had an audible clinical S3, compared with people without a clinical S3, the median CPM device S3 value was numerically greater both before [1.27 AU (1.02 – 7.37) vs 1.18 AU (1.08 – 1.64), p = 0.920] and after dialysis [4.95 AU (1.13 – 8.77) vs 1.28 AU (1.08 – 2.08), p = 0.550] but the differences between groups did not reach statistical significance (**Figure 6-3**). There was no difference between median CPM device thoracic impedance [73.6 ohms (27.7 – 127.7) vs 39.9 ohms (30.7 – 65.0), p = 0.370] or CPM device tidal volume [0.7 ohms (0.5 – 1.0) vs 0.6 ohms (0.3 – 0.7), p = 0.420] in patients who did or did not have an audible S3 on examination before dialysis. This was also the case after dialysis [CPM thoracic impedance: 40.8 ohms (28.2 – 53.4) vs 48.5 ohms (38.6 – 83.4), p = 0.550] and [CPM device tidal volume: 0.7 ohms (0.4 – 0.9) vs 0.7 ohms (0.3 – 0.9), p = 1.000].

Figure 6-3 Bar charts of median CPM S3 (AU) depending on whether a clinical S3 was present or not either before and after dialysis.



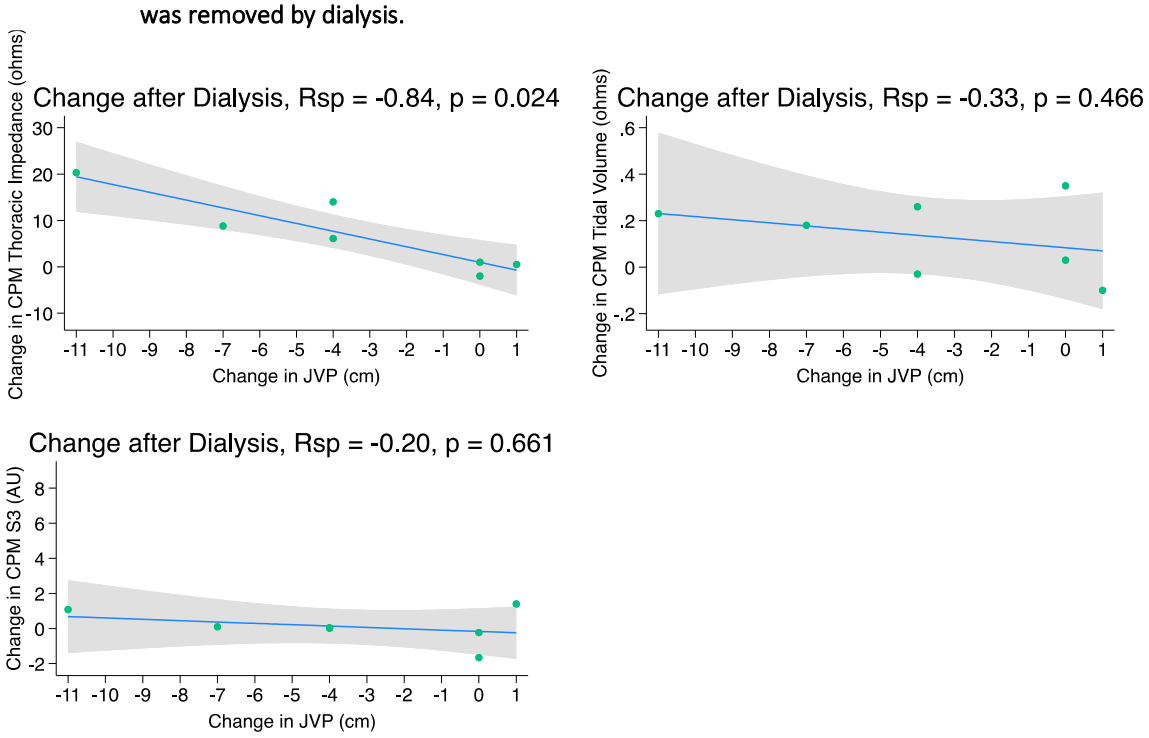
Before dialysis, people who had audible pulmonary rales on examination compared with those without rales, had no difference between CPM device thoracic impedance [42.4 ohms (29.1 – 78.9) vs 39.9 ohms (30.7 – 65.0), p = 0.590] or CPM S3 [1.2 AU (1.1 – 1.6) vs 1.3 AU (1.2 – 3.8), p = 0.230] but CPM device tidal volume was higher in patients without rales [0.5 ohms (0.2 – 1.7) vs 1.1 ohms (0.6 – 1.6), p = 0.013]. After dialysis, there were no differences in CPM device thoracic impedance [53.4 ohms (28.2 – 93.9) vs 43.9 ohms (39.5 – 71.7), p = 0.430], CPM S3 [1.2 AU (1.0 – 2.1) vs 1.4 AU (1.2 – 3.8), p = 0.280] or CPM device tidal volume [0.6 ohms (0.3 – 0.8) vs 0.8 ohms (0.7 – 1.7), p = 0.140] in patients with or without rales.

Before volume was removed by dialysis, among people who had peripheral oedema compared with people who did not, there was no difference in CPM S3 [1.5 AU (1.2 – 3.0) vs 1.2 AU (1.1 – 1.4), p = 0.210], CPM thoracic impedance [30.9 ohms (19.6 – 42.4) vs 57.6 ohms (32.2 – 78.9), p = 0.073] or CPM device tidal volume [0.6 ohms (0.2 – 0.6) vs 0.7 ohms (0.4 – 1.0), p = 0.260]. Again, after dialysis, there were no differences in CPM device thoracic impedance [36.0 ohms (20.5 – 53.4) vs 67.8 ohms (40.4 – 93.9), p = 0.120], CPM S3 [1.4 AU (1.2 – 2.5) vs 1.2 AU (1.0 – 2.1), p = 0.280] and CPM device tidal volume [0.6 ohms (0.4 – 0.7) vs 0.7 ohms (0.3 – 1.1), p = 0.290] in patients with or without peripheral oedema respectively.

Among the 11 patients with an elevated JVP (>4cm), CPM device S3 (r_{sp} = -0.12, p = 0.712), CPM device thoracic impedance (r_{sp} = 0.25, p = 0.252) or CPM device tidal volume (r_{sp} = -0.37, p = 0.256) were poorly correlated with JVP on examination before dialysis. After dialysis, CPM device thoracic impedance and JVP were highly correlated (r_{sp} = -0.84, p = 0.024) but JVP and device S3 (r_{sp} = -0.20, p = 0.661) or tidal volume (r_{sp} = -0.17, p = 0.704) were not. Change in JVP was strongly correlated with change in device thoracic impedance

(r_{sp} = -0.87, p =0.015) but not with change in CPM S3 (r_{sp} = -0.22, p = 0.632), or change in tidal volume (r_{sp} = -0.33, p = 0.466) (**Figure 6-4**).

Figure 6-4 Scatterplots of correlations between change in CPM device measures and change in JVP after fluid was removed by dialysis.



6.3.3.8 Change in clinical symptoms before and after dialysis

6.3.3.8.1 Before dialysis

8 of 21 (38.1%) people self-reported orthopnoea before dialysis. The majority [16 of 21 (76.2%)] of people reported frequent dyspnoea as graded on the EVEREST congestion scale and 4 (19.0%) reported constant breathlessness. When patients were categorized according to NYHA class, 4 (19.0%) had class I symptoms, 5 (23.8%) were in class II, 9 (42.9%) in class III and 3 people were in class IV (14.3%) at baseline. 9 (42.9%) of the cohort reported bendopnea.

6.3.3.8.2 After dialysis

6 of 21 (28.6%) people had orthopnoea after dialysis (p = 0.317). Overall there was an improvement in dyspnoea after dialysis, with no person reporting constant dyspnoea as graded on the EVEREST congestion scale, although 8 people continued to report frequent breathlessness (p = 0.015). When patients were categorized according to NYHA class, 5 (23.8%) had class I symptoms, 10 (47.6%) were now class II and 6 (28.6%) were in class III. No people were in class IV, a difference of 3 people from before dialysis (p = 0.027). 5 patients reported bendopnoea after dialysis (23.8%), a difference of 4 people compared with before dialysis (p = 0.046).

6.3.3.9 Correlation between CPM device measurements and clinical symptoms before and after dialysis

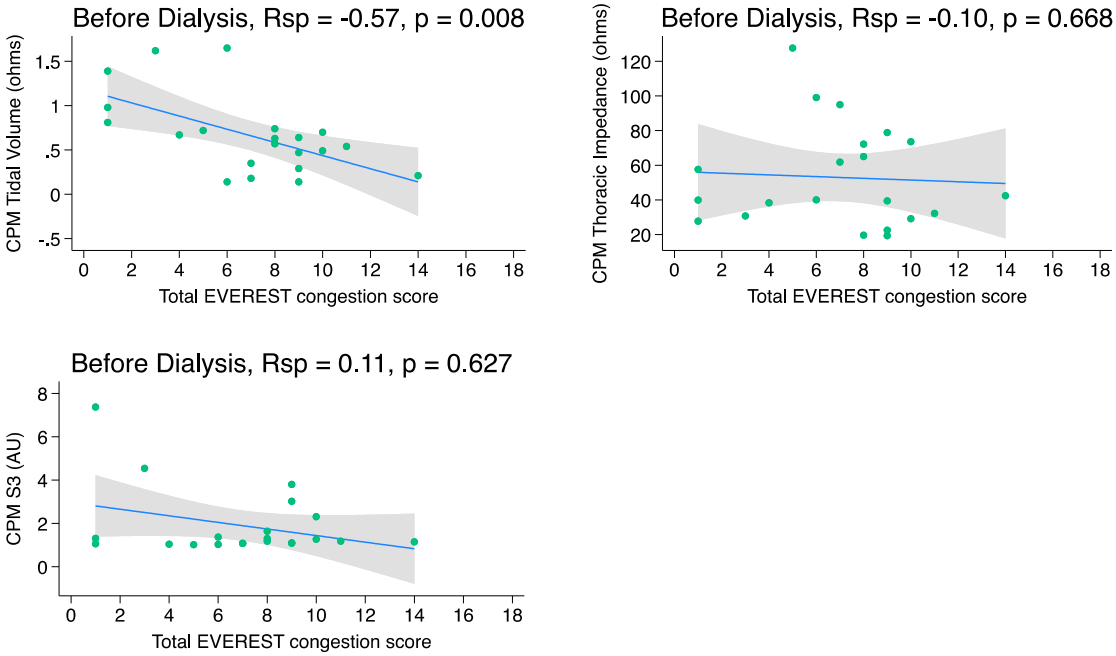
6.3.3.9.1 Before dialysis

There was no difference in CPM device S3 or thoracic impedance across higher grades of the EVEREST dyspnoea scale. An inverse relationship was observed between lower device tidal volume and greater burden of breathlessness (p = 0.031). Total EVEREST congestion score was correlated significantly with CPM device tidal volume (r_{sp} = -0.57, p = 0.008) but not with device thoracic impedance (r_{sp} = -0.10, p = 0.668) or S3 (r_{sp} = 0.11, p = 0.627) (**Figure 6-5**). A similar trend was apparent across NYHA functional classes, although this did not reach statistical significance (**Table 6-7**). There were no differences in any device measures between people who reported orthopnoea or bendopnoea compared with those who did not.

Table 6-7 CPM device measures according to EVEREST dyspnoea grade and NYHA class before dialysis

EVEREST – Dyspnoea grade	**0, N = 5**	**1, N = 4**	**2, N = 8**	**3, N = 4**	**p =**
CPM S3 (AU)	1.3 (1.1 – 4.5)	1.1 (1.1 – 1.7)	1.2 (1.1 – 2.3)	1.2 (1.2 – 1.3)	0.780
CPM Thoracic Impedance (ohms)	39.9 (30.7 - 57.6)	38.9 (33.7 – 50.6)	52.2 (21.5 – 86.9)	53.7 (41.2 – 69.3)	0.750
CPM Tidal Volume (ohms)	1.0 (0.8 – 1.4)	0.6 (0.4 – 0.7)	0.4 (0.2 – 0.6)	0.5 (0.4 – 1.1)	0.031
NYHA class	**1, N = 4**	**2, N = 5**	**3, N = 9**	**4, N = 3**	**p =**
CPM S3 (AU)	1.2 (1.0 – 4.3)	2.3 (1.1 – 3.0)	1.2 (1.1 – 1.4)	1.2 (1.0 – 1.3)	0.670
CPM Thoracic Impedance (ohms)	48.8 (33.8 – 92.7)	30.7 (29.1 – 38.3)	61.8 (32.2 – 72.2)	73.6 (42.4 – 99.1)	0.150
CPM Tidal Volume (ohms)	0.9 (0.8 – 1.2)	0.7 (0.5 – 0.7)	0.6 (0.4 – 0.7)	0.2 (0.1 – 0.5)	0.059

Figure 6-5 Spearman correlations of CPM device measures and total EVEREST congestion score before dialysis.



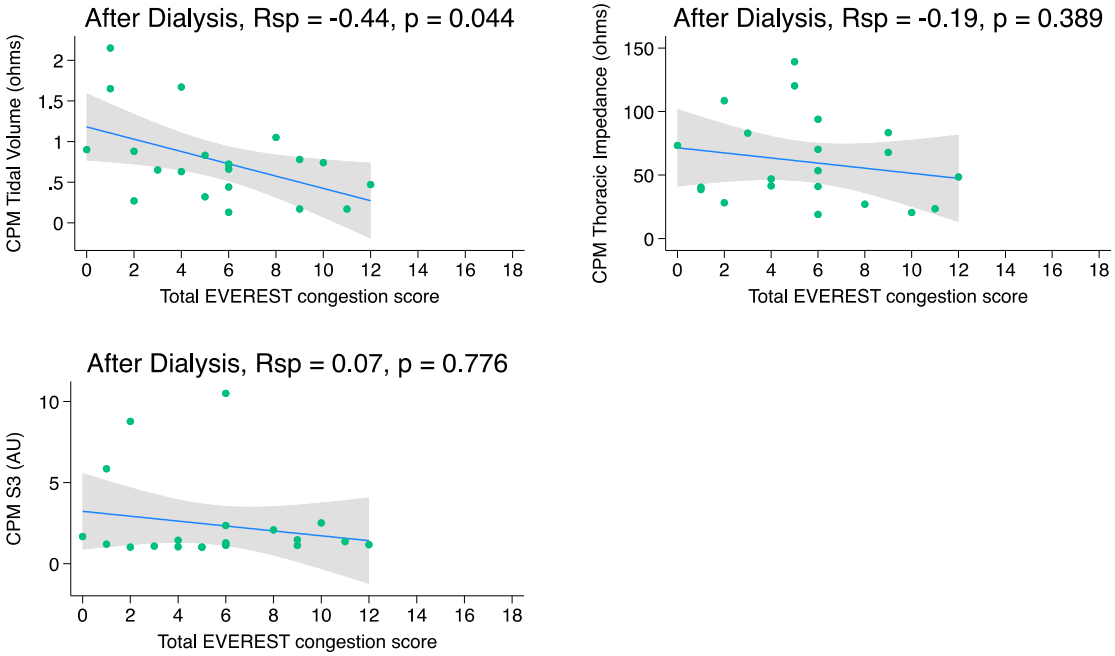
6.3.3.9.2 After dialysis

An inverse relationship was observed between lower device tidal volume and greater burden of breathlessness graded by the EVEREST dyspnoea scale (p = 0.024). Neither CPM device S3 or thoracic impedance differed across grades of the EVEREST dyspnoea scale. After dialysis, total EVEREST congestion score was correlated significantly with CPM device tidal volume (r_{sp} = -0.44, p = 0.044) but not with thoracic impedance (r_{sp} = -0.19, p = 0.389) or device S3 (r_{sp} = 0.07, p = 0.776) (**Figure 6-6**). People in NYHA functional class I had a higher CPM device tidal volume than people in functional classes II or III. CPM device S3 or thoracic impedance did not differ across NYHA groups (**Table 6-8**). Consistent with the analysis before dialysis, there was no difference in any device measures between people who reported orthopnoea or bendopnoea compared with those who did not after dialysis.

Table 6-8 CPM device measures according to EVEREST dyspnoea grade and NYHA class after dialysis

EVEREST – Dyspnoea grade	**0, N = 5**	**1, N = 8**	**2, N = 8**	**3, N = 0**	**p =**
CPM S3 (AU)	1.7 (1.2 – 5.9)	1.1 (1.0 – 1.3)	1.4 (1.2 – 2.4)	-	0.130
CPM Thoracic Impedance (ohms)	40.4 (38.6 – 73.3)	61.8 (44.2 – 95.8)	44.8 (22.0 – 75.6)	-	0.460
CPM Tidal Volume (ohms)	0.9 (0.9 – 1.7)	0.5 (0.3 – 0.9)	0.7 (0.3 – 0.7)	-	0.024
NYHA class	**1, N = 5**	**2, N = 10**	**3, N = 6**	**4, N = 0**	**p =**
CPM S3 (AU)	1.7 (1.2 – 5.6)	1.2 (1.0 – 1.4)	1.4 (1.3 – 2.5)	-	0.210
CPM Thoracic Impedance (ohms)	40.4 (38.6 – 73.3)	61.8 (46.9 – 93.9)	32.3 (20.5 – 67.8)	-	0.180
CPM Tidal Volume (ohms)	0.9 (0.9 – 1.7)	0.6 (0.3 – 0.7)	0.7 (0.2 – 0.7)	-	0.024

Figure 6-6 Spearman correlations of CPM device measures and total EVEREST congestion score after dialysis.



6.3.3.9.3 Correlation between change in CPM device measures and change in symptoms after dialysis

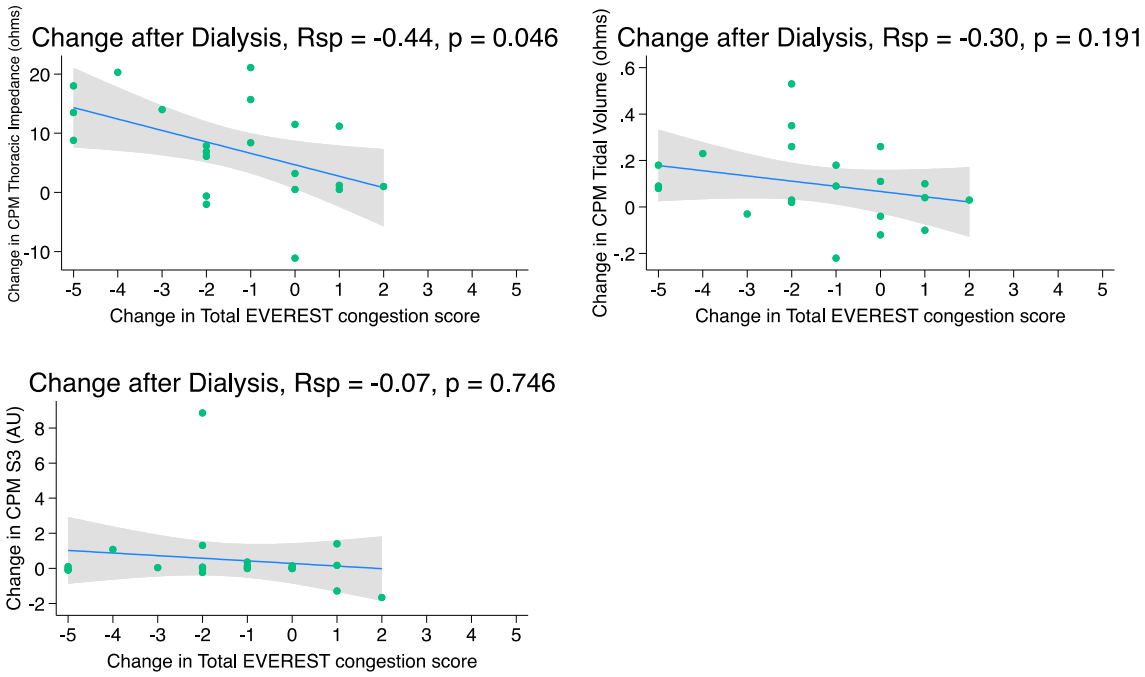
Change in total EVEREST congestion score was correlated significantly with CPM device thoracic impedance (r_{sp} = -0.44, p = 0.046) but not with tidal volume (r_{sp} = -0.30, p = 0.191) or device S3 (r_{sp} = -0.07, p = 0.746) (**Figure 6-7**). People who self-reported an improvement in breathlessness on the EVEREST dyspnoea scale after volume was removed had a substantially higher increase in thoracic impedance compared with people who remained at the same point or had an increase in dyspnoea. There was no difference in change in CPM S3 or change in tidal volume between people who experienced an improvement in EVEREST dyspnoea compared with those who did not (**Table 6-9**). Similar findings in change in CPM device measures were observed when people who had a reduction in NYHA functional class were compared with people who remained in the same or a higher NYHA class after dialysis

(**Table 6-9**). Consistent with the previous analyses before and after dialysis, there was no difference in change in any device measures between people who reported change in orthopnoea or bendopnoea compared with those who did not after dialysis.

Table 6-9 CPM device measures according to change in EVEREST dyspnoea grade and NYHA class after dialysis

Change in EVEREST – Dyspnoea grade	**Decrease, N = 6**	**Same / Increase, N = 15**	**p =**
Change in CPM S3 (AU)	+0.01 (-0.06 to +0.07)	+0.1 (-0.01 to +0.36)	0.390
Change in CPM Thoracic Impedance (ohms)	+15.8 (6.9 – 20.3)	+3.2 (0.5 – 11.2)	0.024
Change in CPM Tidal Volume (ohms)	+0.1 (0.1 – 0.2)	+0.04 (-0.04 to +0.18)	0.330
Change in NYHA class	**Decrease, N = 8**	**Same / Increase, N = 13**	**p =**
Change in CPM S3 (AU)	+0.05 (-0.04 to +0.61)	+0.04 (-0.01 to +0.17)	1.00
Change in CPM Thoracic Impedance (ohms)	+11.0 (+7.4 – +19.2)	+1.2 (+0.5 – +11.2)	0.030
Change in CPM Tidal Volume (ohms)	+0.1 (+0.05 to +0.25)	+0.04 (-0.03 to +0.11)	0.360

Figure 6-7 Spearman correlations between change in CPM device measures and change in total EVEREST congestion score



6.3.3.10 Change in congestion biomarkers before and after dialysis

All 21 patients had NT-proBNP and MR-proANP measured before and after dialysis. Haematocrit, measured as part of standard clinical care, was collected in 20 people before dialysis and 18 after dialysis. Change in haematocrit was therefore calculated in 18 people. The median NT-proBNP was 43624 pg/ml (4955 - 88720) before dialysis and 37681 pg/ml (6666 - 70666) after volume was removed (p value for difference = 0.046). Change in NT-proBNP did not correlate significantly with volume of fluid removed by dialysis (r_{sp} = 0.16, p = 0.493).

The median MR-proANP was 1251 pmol/L (670 - 1859) before dialysis and 1250 pmol/L (664 - 1673) after volume was removed (p = 0.305). Change in MR-proANP did not correlate significantly with volume of fluid removed by dialysis (r_{sp} = 0.17, p = 0.471).

The median haematocrit value was 0.31 L/L (0.27 – 0.33) before dialysis and 0.29 L/L (0.27 – 0.34) after volume was removed (p = 0.037). Change in haematocrit did not correlate significantly with volume of fluid removed by dialysis (r_{sp} = 0.14, p = 0.567).

6.3.3.10.1 Correlation between congestion biomarkers and CPM device measurements before and after dialysis

In biomarkers measured before dialysis, CPM device S3 was significantly correlated with NT-proBNP (r_{sp} = 0.46, p = 0.035) and MR-proANP (r_{sp} = 0.52, p = 0.016) but not with haematocrit (r_{sp} = 0.07, p = 0.760). CPM device thoracic impedance was inversely correlated with NT-proBNP (-0.55, p = 0.011) and MR-proANP (r_{sp} = -0.66, p = 0.001) but not haematocrit (r_{sp} = 0.20, p = 0.385). CPM device tidal volume was not significantly correlated with NT-proBNP (r_{sp} = -0.01, p = 0.964), MR-proANP (r_{sp} = -0.03, p = 0.913) or haematocrit (r_{sp} = 0.04, p = 0.878).

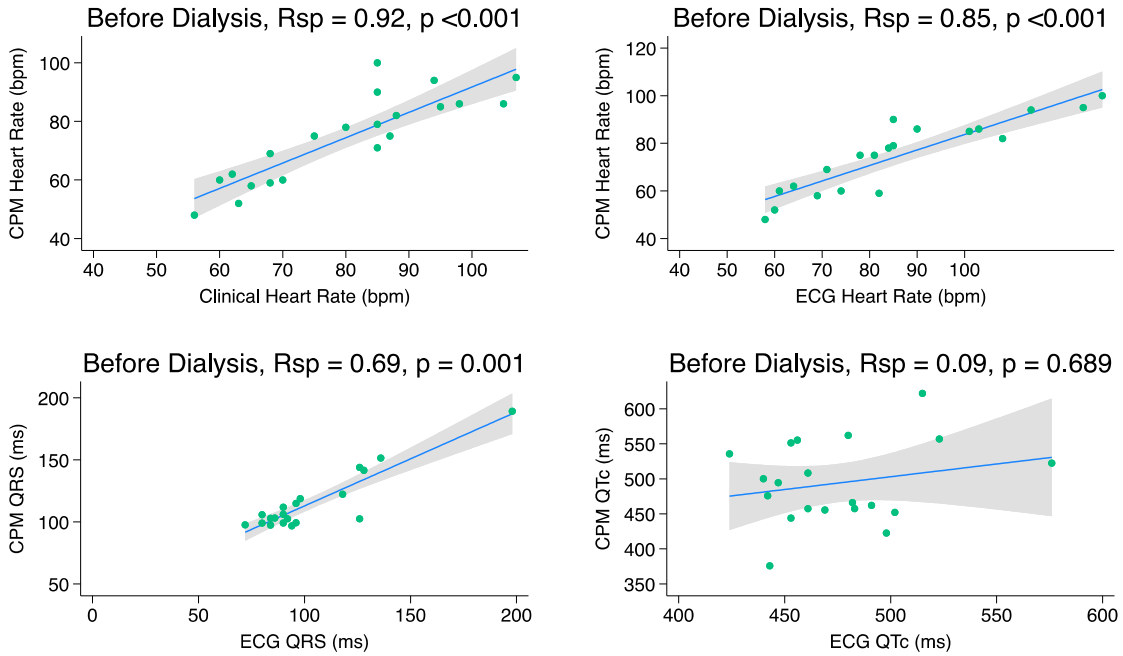
When measured after dialysis, CPM device S3 was no longer correlated with NT-proBNP (r_{sp} = 0.23, p = 0.308), MR-proANP (r_{sp} = 0.31, p = 0.170) or haematocrit (r_{sp} = 0.04, p = 0.878). CPM device thoracic impedance remained inversely correlated with NT-proBNP (-0.49, p = 0.025) and MR-proANP (r_{sp} = -0.58, p = 0.007) but not with haematocrit (r_{sp} = 0.33, p = 0.182). After dialysis, CPM device tidal volume was not significantly correlated with NT-proBNP (r_{sp} = -0.002, p = 0.993), MR-proANP (r_{sp} = 0.08, p = 0.737) or haematocrit (r_{sp} = 0.09, p = 0.730).

When calculated change in CPM device measures was analysed with change in biomarkers after dialysis, there were no significant correlations between device S3 and NT-proBNP (r_{sp} = -0.05, p = 0.824), MR-proANP (r_{sp} = 0.05, p = 0.824) or haematocrit (r_{sp} = 0.19, p = 0.447), or between thoracic impedance and NT-proBNP (r_{sp} = -0.08, p = 0.752), MR-proANP (r_{sp} = -0.05, p = 0.824) or haematocrit (r_{sp} = 0.37, p = 0.132). Similarly, change in CPM device tidal volume was not correlated with change in NT-proBNP (r_{sp} = -0.18, p = 0.430), MR-proANP (r_{sp} = 0.24, p = 0.300) or haematocrit (r_{sp} = 0.20, p = 0.419).

6.3.3.11 Correlation between CPM device measurements and clinical heart rate and surface ECG

The median heart rate on clinical examination was 85 bpm (68 - 88). 20 of 21 people had a baseline ECG performed. CPM device heart rate and heart rate on clinical examination were strongly correlated (r_{sp} = 0.85, p <0.001). CPM device heart rate and ECG heart rate were strongly correlated (r_{sp} = 0.92, p <0.001). The median ECG QRS duration was 93 milliseconds (85 - 122). CPM device QRS and ECG QRS duration were correlated (r_{sp} = 0.69, p = 0.001). ECG and CPM device corrected QT intervals were not correlated (r_{sp} = 0.09, p = 0.689). (**Figure 6-8**)

Figure 6-8 Spearman correlations of CPM device measures with clinical heart rate and surface ECG measures.



After dialysis, CPM device heart rate and clinical heart rate remained strongly correlated (r_{sp} = 0.87, p < 0.001).

On clinical examination, 4 of 21 people (19.0%) had an irregular pulse. When the relationship between the CPM device heart rhythm algorithm and heart rate regularity on clinical examination was analysed there was a high level of agreement between measures obtained before dialysis (Kappa = 0.82, p < 0.001). When analysed after dialysis, 5 people had an irregular pulse. The degree of agreement between the CPM device rhythm algorithm and heart rate regularity remained strong but was weaker than before dialysis (Kappa = 0.70, p < 0.001).

6.3.3.12 Adverse Events

There were no device related adverse events in this study cohort, including no evidence of device-device interaction in any patients with an implanted cardiac device.

6.3.3.13 Device Deficiencies

One device deficiency was reported due to an inability to map a device to a patient ID as detailed below. ADI were contacted and the device mapping issue was promptly resolved.

Date	Device ID	Patient ID	Type of Incident	When deficiency was identified	Action taken
26/03/2022	ADI11613-3	02023	Procedure (Use of the device) - Device remained mapped to a previous participant ID despite having been returned by Analog Devices Inc and previous patient's data cleaned from it.	During use	Analog Devices Inc were contacted at the time and the previous patient's ID was de-mapped from the app so that the study ID for patient 02023 could be mapped to the device ID.

6.4 Discussion

In this cohort of patients with established end-stage renal disease undergoing haemodialysis there was a high prevalence of cardiovascular disease with the majority of people having at least one risk factor despite being relatively young (mean age 60 years). 71% of people had hypertension and 28% had a history of atrial fibrillation or diabetes. Approximately 24% had a diagnosis of HF and 1 in 5 patients had had a MI. As such, they were people who either had established HF or, with the additional factor of being dialysis-dependent and chronically uraemic, were at heightened risk for the development of HF. Compared with the two other cohorts enrolled in the CONGEST-HF study, these people had milder systolic dysfunction on echocardiogram, with a mean LVEF 48% ± 17 [median LVEF was 55% (30 - 60)].

Considering that these people were not necessarily admitted to hospital for fluid excess, symptoms of volume overload were still commonly self-reported, a testament to the state of chronic congestion that dialysis dependency presents. The majority of people had breathlessness and approximately 40% had either bendopnoea or orthopnoea. On examination at baseline, the majority of patients had features of congestion, including rales (71.4%) and an elevated JVP (52.4%). Interestingly, relative to cohort C, fewer people had peripheral oedema. Peripheral oedema is a cardinal feature of tissue congestion which often presents, particularly in younger people, as a late feature when substantial amounts of excess volume has accumulated. Few people had a clinically detectable S3 either before or after dialysis and therefore limited the ability to examine the relationship between S3 on auscultation and device measures. Both CPM thoracic impedance and tidal volume increased when volume was removed by dialysis indicating a decongestion of lung tissue. That thoracic impedance may be sensitive to shifts in total body fluid volume is supported by

the correlation observed between change in thoracic impedance and the more global grading of congestion in the total EVEREST score whereas CPM tidal volume, being more susceptible to specific congestion effects on the airways was correlated with dyspnoea and (before dialysis) pulmonary rales.

In keeping with several prior reports, median LAVI was substantially elevated indicating chronically raised filling pressures in people who likely experienced episodic overt or frequent subclinical levels of congestion[295-297]. LV GLS has been observed in other studies to be reduced in patients receiving dialysis compared to healthy controls irrespective of LVEF[298,299], a finding that was also present in the current study cohort. The remaining echocardiographic parameters were largely within normal range at baseline, including IVC diameter, TR vmax and an intermediate value for E/e' ratio depending on the international guidelines[114]. E/A ratio may be pseudo-normalized in patients with diastolic dysfunction which is often present in people with chronic kidney disease[300,301]. With marked LAVI enlargement in this study cohort, elevated filling pressures and impaired myocardial relaxation was highly likely. A minor but statistically significant reduction in E/A ratio occurred following dialysis that may have been related to an improvement in left ventricular wall stress. In this context, the three echocardiographic parameters (TR vmax, LAVI and E/A ratio) that demonstrated change between study intervals were haemodynamically related rather than indices of left ventricular performance. The probability of fixed pulmonary hypertension was low in this population, with PVAT within normal range and TR vmax demonstrated sensitivity to changes in congestion by also correlating with the volume of fluid removed by dialysis. When correlated with the CPM device measures a pattern emerged where measures of left ventricular filling (LAVI) or performance (LV GLS) correlated

with CPM device S3 and echocardiographic estimations of intra-pulmonary pressures and congestion (TR vmax, PVAT) correlated with device thoracic impedance or tidal volume. The minimal extent to which echocardiographic measures changed after dialysis restricted the ability to detect correlations with changes in the device parameters.

The concentrations of both natriuretic peptides, NT-proBNP and MR-proANP, were markedly elevated. While this is anticipated in patients who were on dialysis, the median value of NT-proBNP of 43,624 pg/ml was higher even than several other reports of concentrations in this population[302-304]. The correlation between NT-proBNP and invasive intra-cardiac filling pressures has not been well-described in people receiving dialysis. However, only 25% of NT-proBNP clearance is via the kidneys[209,210] and NT-proBNP was observed both in prior reports[302,305] and in this study to reduce following dialysis. Intravascular congestion results from raised intra-cardiopulmonary pressures, inducing the release of NT-proBNP when left ventricular wall stress rises. Conversely NT-proBNP concentration might be more sensitive to a reduction in pressure and wall stress when fluid is offloaded by dialysis rather than necessarily the degree to which patients are decongested as the volume removed and change in NT-proBNP levels have previously, and in this current study, been shown to correlate poorly[306,307]. When patients were most volume replete, under the conditions with the greatest degree of left ventricular wall stress, both MR-proANP and NT-proANP correlated with CPM device S3. Following volume removal, largely from the intravascular compartment during haemodialysis, wall stress is likely to have reduced and the strength of the correlations diminished, suggesting that in this cohort the CPM device S3 performed better where conditions of left ventricular wall stress or filling pressure elevation was present. CPM thoracic impedance, which inversely correlated with both natriuretic peptides

before and after dialysis, appears to be more sensitive to a broader range of congestion markers than CPM device S3, possibly because changes in left ventricular filling pressures or intravascular haemodynamics can also influence extravascular, interstitial fluid accumulation in the lungs and peripheral tissues. The relationship between higher intra-cardiac filling pressures and greater pulmonary tissue congestion is supported by the CPM device S3 correlating with LUS B-lines before dialysis. The correlations between device S3 and B-lines after dialysis and when change in both of these parameters was analysed were slightly weaker and narrowly above the pre-defined threshold for statistical significance. As I will explain below, the sample size may not have been sufficient to establish correlations when small changes in parameters were present. This has added relevance in analyses of change for CPM S3 which did not differ substantially between study assessments.

The standard dialysis session in this study lasted 4 hours. During this relatively short period of time a notable amount of fluid (2L) was removed. Compared with Cohort C of the CONGEST-HF study, in whom the median weight loss in the first 24 hours was only 0.3kg, the people in Cohort B were decongested more rapidly and to a greater extent between the initial study intervals. Within the first 24 hours of Cohort C, LUS B-lines reduced from a median of 80 to 68 ($p = 0.002$), a 15% reduction from baseline. In Cohort B the percentage reduction in B-lines within 4 hours was 46.6%. The presence of pulmonary congestion reflected by LUS B-lines has already been examined in several studies where reductions in B-lines have been demonstrated in patients after dialysis[105,292,308]. Mean pre-dialysis B-lines count in these studies was reported between 16.0 ± 5.53 to 24.0 ± 25.0. In the current study, the LUS B-line count was considerably higher, with a median pre-dialysis count of 58 (33 - 94) and a post-dialysis count of 31 (15 - 67). This sizeable 46.6% reduction

in B-lines followed an average removal of 2L of fluid, yet despite such a seemingly evident dose-response relationship the volume of fluid removed and change in B-lines did not correlate significantly. Potential individual variation in the rate at which lymphatics can clear fluid from the lungs may account for this lack of an apparent relationship yet previous work has also reported differences in the strength of correlations between measures of body volume estimated by body impedance, weight gain between dialysis sessions or fluid removed during dialysis and pulmonary congestion reflected by B-lines[105,308-310]. The indication is that, as with some patients with HF, fluid accumulation within the lungs in patients receiving dialysis is not solely attributable to excess systemic fluid but may also be determined by conditions of redistribution or impaired permeability across the alveolar-capillary membrane into the interstitial space. Differences in compartmental congestion was supported at the bedside in this study cohort by the difference in prevalence of features of tissue congestion such as peripheral oedema compared with pulmonary congestion evidenced by rales.

Thoracic bioimpedance has already been examined in patients receiving dialysis demonstrating inverse correlations with volume of fluid removed[311-313]. One study of 25 patients receiving dialysis reported a Spearman correlation coefficient as high as $r_{sp} = 0.96$, $p<0.001$ between change in thoracic impedance and volume of fluid removed, where the mean volume removed was 3.4L ± 1.2 and the thoracic impedance correspondingly increased by 21%[314]. Analyses of total body impedance in patients with dialysis showed that fluid often accumulates in the extracellular compartment and therefore changes in impedance are more likely to be sensitive to shifts in extracellular fluid than changes in intravascular volume[314,315]. In the current cohort, the volume of fluid removed while

clinically relevant was 1.4L less than in the aforementioned study and the change in thoracic impedance was also lower with a 12% increase that was nonetheless statistically significant. Differences between studies in the strengths of correlations between thoracic impedance and the volume of fluid removed may be related to internal differences in the cohorts and effectiveness of the devices examined. An additional point of consideration is that the correlation between CPM device thoracic impedance and volume of fluid removed was more modest in the current study (r_{sp} = 0.49, p = 0.024) because a greater degree of intravascular volume removal was required to impact fluid stored in the extracellular compartment. The smaller the degree of change the less robust the correlation appeared. This hypothesis also had important implications for the interpretation of the correlation between CPM device thoracic impedance and LUS, which represents extravascular lung water. CPM device thoracic impedance was strongly correlated with LUS B-lines both before and after dialysis. The strength of the correlation was greater after fluid was removed, an observation also seen in Cohort C where device thoracic impedance appeared most sensitive to fluid status the more euvolaemic and extravascularly deplete patients became. However, change in device thoracic impedance showed no meaningful correlation with change in LUS. By calculating change in both parameters, the range of values in the change variables was reduced relative to the absolute values obtained before and after dialysis as shown in the **Table 6-10** below. To either increase the strength of the correlation or reduce the uncertainty that the correlation was a chance finding, a greater range of change values would likely have been required and by necessity would have been achieved by having a larger cohort sample size.

Table 6-10 Summary of descriptive statistics of the CPM thoracic impedance and LUS variables

Variable	Observations	Mean	SD	Median	IQR	Min	Max
B-lines pre-dialysis	21	71.2	55.3	58	33 – 94	5	209
B-lines post-dialysis	21	47.8	45.7	31	15 – 67	0	165
Change in B-lines	21	-23.4	27.0	-18	-38 to -5	-88.0	28
Impedance pre-dialysis	21	52.9	29.5	40.0	30.7 – 72.2	19.3	127.7
Impedance post-dialysis	21	60.4	34.2	48.5	38.6 – 83.0	19.0	139.2
Change in impedance	21	7.4	8.2	7.9	1.0 – 13.5	-11.1	21.1

IQR = interquartile range; Min = minimum; Max = maximum; SD = standard deviation; TI = thoracic impedance

As in other cohorts in CONGEST-HF, in this study the correlations between CPM device and heart rate and ECG parameters, including the Rhythm detection algorithm and pulse regularity, were strong. It cannot be discounted that some patients who had an irregular pulse due to premature ventricular contractions would have been assigned a (appropriate) negative Rhythm result, thereby underestimating the agreement between both measures.

6.5 Limitations

The limitations of this study are similar to those described in the other CONGEST-HF cohorts, namely spirometry and CPM device tidal volumes were not measured at the same time and it cannot be discounted therefore that depth and rapidity of breathing changed between readings. As described above, the sample size could have limited the ability to establish correlations between device and clinical measures and the statistical significance of the analyses. The degree of change in several variables after dialysis was either minor or negligible and making it difficult to detect correlations in a number of analyses, particularly those examining echocardiography and physical signs or symptoms. A high number of tests were performed with no correction for multiple testing. I will discuss the impact of the COVID pandemic on the study later in the General Discussion chapter.

6.6 Conclusions

In this study, examining the effectiveness of the CPM device to detect congestion in patients with end-stage renal disease on dialysis, I found that device thoracic impedance was strongly correlated with extravascular lung water as reflected by LUS B-lines. Thoracic impedance was also correlated with a broader range of congestion parameters reflecting left ventricular filling pressures or systemic, peripheral congestion. While thoracic impedance is a parameter most directed to extravascular congestion within the lungs, it also appears to be a marker for broader shifts of fluid within the interstitium and can be modified by intravascular haemodynamics. CPM device S3 and device tidal volume

correlated more specifically with measures of left ventricular filling pressures and wall stress or pulmonary congestion respectively.

7. CHAPTER SEVEN. A study of the non-invasive CardioPulmonary Management (CPM) device in patient admitted to hospital with heart failure who were receiving intravenous diuretics

7.1 Introduction

The development of overt congestion, manifested by features such as worsening breathlessness or oedema, remains the principal driver for hospitalization for HF. As described in the Introduction chapter of this thesis, the haemodynamic changes that lead to the development of clinically apparent congestion often occur weeks to months prior to the patient presenting to their healthcare provider. Conversely, relief of symptoms such as dyspnoea or objective evidence of decongestion such as reduction in LUS B-lines can be achieved within hours of treatment being initiated[316-318]. Yet many patients are discharged with residual congestion and rehospitalization rates among these patients are high[17]. The ubiquitous persistence of congestion on discharge and the profound implications this has for patient outcomes makes being able to accurately determine congestion and changes in congestion in such people a clinical imperative.

In this study, to be able to capture changes in congestion at important stages of treatment during admission, I examined across four intervals whether the CPM device measures correlated with change in weight and B-lines on LUS as well as serial measures of spirometry, clinical signs and symptoms, echocardiography, biomarkers and ECG. This study was designed to examine the ability of the CPM device to detect congestion and changes in congestion in a typical, high risk HF population. The aim of the study was to recruit patients

as close to the point of greatest congestion and sequentially assess these people while a state of euvolaemia was achieved, representing a “wet-to-dry” process.

7.2 Methods

The inclusion and exclusion criteria and study objective for Cohort C were detailed in **Chapter 4**. All patients were recruited while inpatients under the Cardiology service at the QEUH, Glasgow and were studied while receiving care in the Acute Receiving Units, Coronary Care Unit or Wards 6C and 6D.

7.2.1 Study procedures

CPM device readings and data transfer, echocardiography, LUS, spirometry, blood phlebotomy and analyses were all carried out in accordance with the CONGEST-HF study standard operating procedures (**Appendix**). A study assessment was performed on study day one as early in the admission as possible and after 12 hours from initial approach to allow the patient to decide if they wanted to take part. The second study assessment was performed the following day while the patient was still IV diuretics. The third visit took place on the day the patient switched to oral diuretics (had the first dose) and the final fourth visit was conducted on the day of discharge.

7.2.2 Statistical Analyses

Continuous variables were summarised using the mean and standard deviation (SD) or median with inter-quartile ranges (IQR) depending on the normality of the data. Categorical variables are summarised with frequencies and percentages. Individual-patient Spearman

correlations were used to determine the correlations between device measurements and clinical parameters that were continuous variables, with scatter plots provided to graphically represent the correlation. Relations between continuous and categorical variables were analysed using Mann-Whitney-Wilcoxon tests or Kruskal-Wallis tests as appropriate. The Wilcoxon signed rank test was used to analyse the relationship between continuous variables measured before and after study intervals. McNemar's test was used to examine the relationship between categorical variables before and after study intervals. In addition, where a CPM reading represented the same quantity as a categorical variable, outcomes were compared using weighted kappa statistics. A p value <0.05 was considered statistically significant. Analyses were performed using STATA version 18 (College Station, Texas, USA).

7.3 Results

25 patients with a primary diagnosis of heart failure on admission to hospital were recruited in this study. The study was conducted between 29th November 2021 and 13th July 2022. The median time to switch from IV to oral diuretics was 4 days (3 - 5) and median time from enrolment to discharge was 7 days (4 - 14). As expected in a broader population of people with HF, patients in this cohort were older than Cohort A, with a mean age of 72.8 ± 12.5. Ischaemic cardiomyopathy was the most frequent cause for HF and approximately half of the cohort had been hospitalized for HF previously. As expected given the cause of presentation to hospital, the majority of people were highly symptomatic when enrolled with 72% being NYHA functional class III or IV. Most patients had left ventricular systolic impairment with a mean LVEF 31% ± 15 and a prognostically important NT-proBNP at baseline [3899 pg/ml (1567 - 9151)]. 4 of 25 (16%) people had an implanted device,

including 2 of whom had ICDs and 2 had conventional pacemakers. Baseline characteristics are summarised in **Table 7-1**.

Table 7-1 Baseline characteristics of patients enrolled in Cohort C of the CONGEST-HF study

N =	25
Male sex (%)	18 (72.0)
Age (years)	72.8 ± 12.5
Race (%)	
White	23 (92)
Black	-
Asian	2 (8)
Other	-
BMI (kg/m^2)	29.1 ± 5.0
Medical History (%)	
Hypertension	12 (48)
Diabetes	7 (28)
AF on baseline ECG	7 (30)
History of any AF	12 (48.0)
MI	7 (28.0)
Stroke	4 (16.0)
COPD	3 (12)
LVEF (%)	31 ± 15
NYHA Class (%)	
I	-

II	7 (28.0)
III	10 (40.0)
IV	8 (32.0)
Symptoms/signs (%)	
Dyspnoea	25 (100)
Orthopnoea	13 (52)
PND	4 (16)
Fatigue	21 (84)
Bendopnoea	11 (44)
Peripheral oedema	22 (88.0)
Systolic BP (mmHg)	121 ± 25
Heart rate (bpm)	79 ± 17
Respiratory rate (per min)	17 ± 2
Chest circumference (cm)	108 ± 13
Duration of HF	
<1 year	9 (36.0)
1 – 5 years	13 (52.0)
>5 years	3 (12.0)
Ischaemic aetiology (%)	11 (44.0)
Prior HF Hospitalization (%)	13 (52.0)
HF Hospitalization within previous 6 months (%)	6 (24.0)

NT-proBNP (pg/ml)	3899 (1567 - 9151)
MR-proANP (pmol/L)	487 (367 - 595)
eGFR (mL/min/1.73m^2)	49 (33 - 69)
Haematocrit (L/L)	0.38 ± 0.1
ECG – sinus (%)	16 (64.0)
ECG – AF (%)	7 (28.0)
ECG – Paced rhythm (%)	1 (4.0)
Baseline treatment (%)	
Loop diuretic	25 (100.0)
Thiazide / Thiazide-like diuretic	0 (0.0)
ACE inhibitor or Angiotensin Receptor Blocker	8 (32.0)
Sacubitril / Valsartan	6 (24.0)
Beta-blocker	17 (68.0)
MRA	9 (36.0)
SGLT2 inhibitor	11 (44.0)
Digoxin	1 (4.0)
Any implanted device	4 (16)
ICD	2 (8.0)
CRT-D	0 (0.0)
CRT-P	0 (0.0)

Pacemaker	2 (8.0)
Loop recorder	0 (0.0)

ACE = angiotensin converting enzyme; AF = atrial fibrillation; BMI = body mass index; COPD = chronic obstructive pulmonary disease; CRT-D = cardiac resynchronization therapy-defibrillator; CRT-P = cardiac resynchronization therapy-pacemaker; ECG = electrocardiogram; eGFR = estimated glomerular filtration rate; HF = heart failure; ICD = implantable cardioverter defibrillator; LVEF = left ventricular ejection fraction; MI = myocardial infarction; MRA = mineralocorticoid receptor antagonist; MR-proANP = mid regional pro-atrial natriuretic peptide; NT-proBNP = n-terminal pro-B type natriuretic peptide; NYHA = New York Heart Association; PND = paroxysmal nocturnal dyspnoea; SGLT2 = sodium glucose co-transporter 2.

7.3.1 Change in weight correlated with other clinical measures

During the standard care being provided to these patients, weight was the principal objective parameter used by their responsible medical team to gauge the extent of decongestion. Weight was measured in all patients at each study assessment undertaken. The mean change in weight per study interval was; -0.3kg $\pm$ 3.3, $p = 0.035$, for change from day 1 to day 2 on IV diuretics; -3.5kg $\pm$ 5.3, $p < 0.001$, for change from day 1 on IV diuretics to first day of oral diuretics; - 3.7kg $\pm$ 5.5, $p < 0.001$, for change from day 1 on IV diuretics to day of discharge.

When change in weight was correlated with change in the clinical variables collected as part of the study, the strength of the correlations observed was generally weak. Change in weight was significantly correlated with change in LAVI on echocardiography between study visit 1 and visit 2 on IV diuretics, change in LV GLS between visit 1 on IV diuretics and day of discharge, change in IVC diameter between study visit 1 and visit 2 on IV diuretics, and with change in total EVEREST congestion score at each interval (**Table 7-2**). Change in weight was not significantly correlated with change in B-lines on LUS, change in NT-proBNP, change in MR-proANP, change in haematocrit, change in JVP elevation, or change in other echocardiographic parameters (**Table 7-2)**.

7.3.2 Change in CPM device measures across study visits during admission

The absolute values for CPM device S3, thoracic impedance and tidal volume as well as p values for difference with the values obtained on day 1 of IV diuretics are reported for the subsequent study assessments in **Table 7-3**. Thoracic impedance increased steadily until the day of first dose oral diuretics (study visit 3) but had decreased by discharge. There was no apparent difference in CPM S3 or tidal volume across the study visits compared with baseline.

Table 7-2 Spearman correlations between change in weight and clinical parameters

Clinical Parameter	Visit 1 to Visit 2 on IV diuretics. Change in Weight Rsp = , p Value	Visit 1 on IV diuretics to 1st dose oral diuretics. Change in Weight Rsp = , p Value	Visit 1 on IV diuretics to day of discharge. Change in Weight Rsp = , p Value
Change in EVEREST total congestion score	0.45, p = 0.032	0.52, p = 0.008	0.47, p = 0.031
Change in IVC diameter (mm)	-0.56, p = 0.013	-0.07, p = 0.749	0.03, p = 0.906
Change in LV GLS (%)	-0.19, p = 0.456	-0.34, p = 0.144	-0.56, p = 0.049
Change in LUS B-lines (n =)	0.21, p = 0.326	0.34, p = 0.095	0.03, p = 0.901
Change in NT-proBNP (pg/ml)	-0.02, p = 0.933	-0.13, p = 0.556	-0.10, p = 0.655
Change in MR-proANP (pmol/L)	-0.25, p = 0.258	-0.30, p = 0.151	-0.42, p = 0.059
Change in Haematocrit (L/L)	0.18, p = 0.450	-0.42, p = 0.063	-0.19, p = 0.472
Change in JVP elevation (cm)	0.42, p = 0.107	-0.24, p = 0.422	0.10, p = 0.868
Change in LVEF (%)	-0.02, p = 0.934	-0.28, p = 0.180	-0.28, p = 0.211

Change in PVAT (ms)	-0.02, p = 0.932	-0.02, p = 0.933	-0.01, p = 0.957
Change in TR Vmax (m/s)	0.26, p = 0.224	-0.11, p = 0.584	-0.06, p = 0.797
Change in LAVI (ml/m^2)	-0.02, p = 0.912	0.29, p = 0.167	0.01, p = 0.966
Change in MV inflow deceleration (ms)	-0.25, p = 0.247	-0.16, p = 0.455	-0.12, p = 0.617
Change in LVOT VTI (cm)	0.10, p = 0.663	0.007, p = 0.976	-0.14, p = 0.564

Table 7-3 CPM device parameter values across interval study visits

CPM Device Parameter	Visit 1 on IV diuretics	Visit 2 on IV diuretics	*p =	1st dose oral diuretics	*p =	Day of discharge	*p =
Thoracic Impedance (ohms)	70.8 (39.7 – 93.4)	75.1 (39.3 – 98.8)	0.311	78.5 (46.2 – 104.5)	0.048	66.5 (48.2 – 99.4)	0.297
S3 (AU)	1.4 (1.1 – 1.8)	1.3 (1.1 – 2.7)	0.107	1.5 (1.2 – 2.5)	0.788	1.3 (1.2 – 2.3)	0.794
Tidal Volume (ohms)	0.48 (0.29 – 0.69)	0.45 (0.28 – 0.90)	0.649	0.46 (0.35 – 0.67)	0.587	0.49 (0.32 – 0.73)	0.658

*p value for difference with baseline Visit 1 on IV diuretics

7.3.3 Primary analyses

7.3.3.1 Correlation between CPM device thoracic impedance and LUS B-lines and change in thoracic impedance and change in B-lines

All 25 patients had LUS performed at each study assessment. The median number of B-lines [n = (IQR)] per study visit incrementally reduced from the first assessment onwards; day 1 on IV diuretics: n = 80 (49 - 124); day 2 on IV diuretics: n = 68 (43 - 98), p value for difference with visit 1 = 0.002 ; day of 1st oral diuretic: n = 56 (37 - 80), p value for difference with visit 1 = 0.002; day of discharge: n = 44 (24 – 59), p value for difference with visit 1 < 0.001.

When analysed at each corresponding study interval, CPM device thoracic impedance did not correlate significantly with B-lines on LUS (**Table 7-4) (Figure 7-1)**. Change in device thoracic impedance did not correlate with respective change in B-lines (**Table 7-5) (Figure 7-2).**

Table 7-4 Spearman correlations between CPM device thoracic impedance and LUS B-lines per study visit

	Visit 1 on IV diuretics. LUS B-lines Rsp = , p Value	**Visit 2 on IV diuretics. LUS B-lines Rsp = , p Value**	**1st dose oral diuretics. LUS B-lines Rsp = , p Value**	**Day of discharge. LUS B-lines Rsp = , p Value**
CPM device thoracic impedance	0.12, p = 0.553	-0.005, p = 0.982	-0.38, p = 0.064	-0.31, p = 0.167

Figure 7-1 Spearman correlations of CPM device thoracic impedance and LUS B-lines

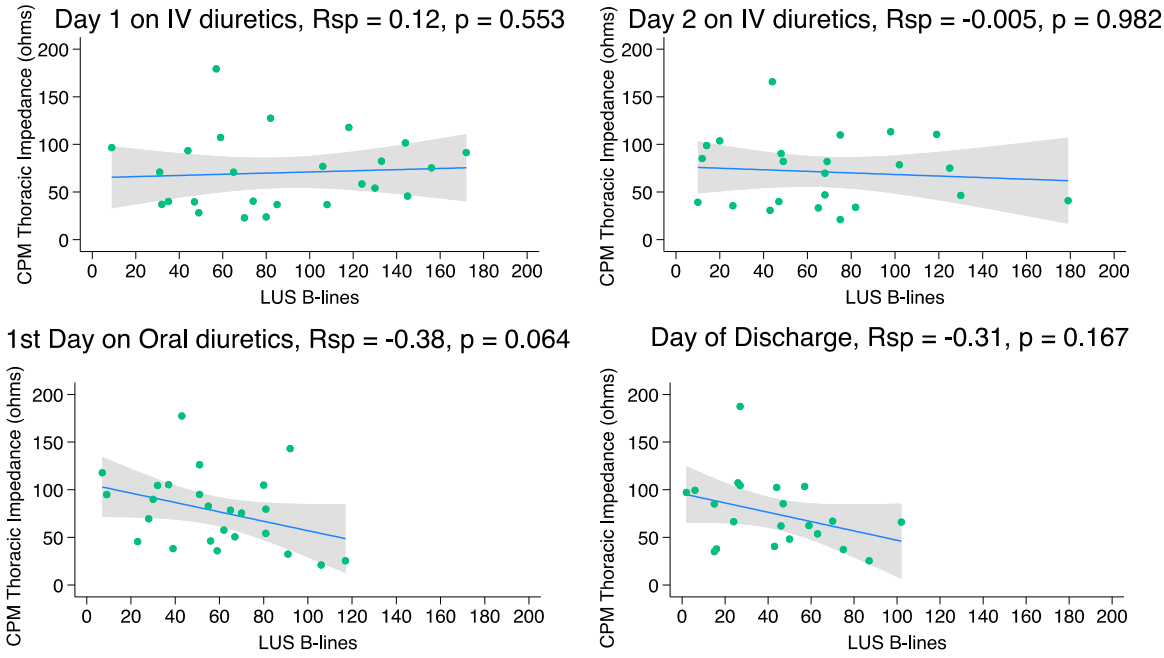
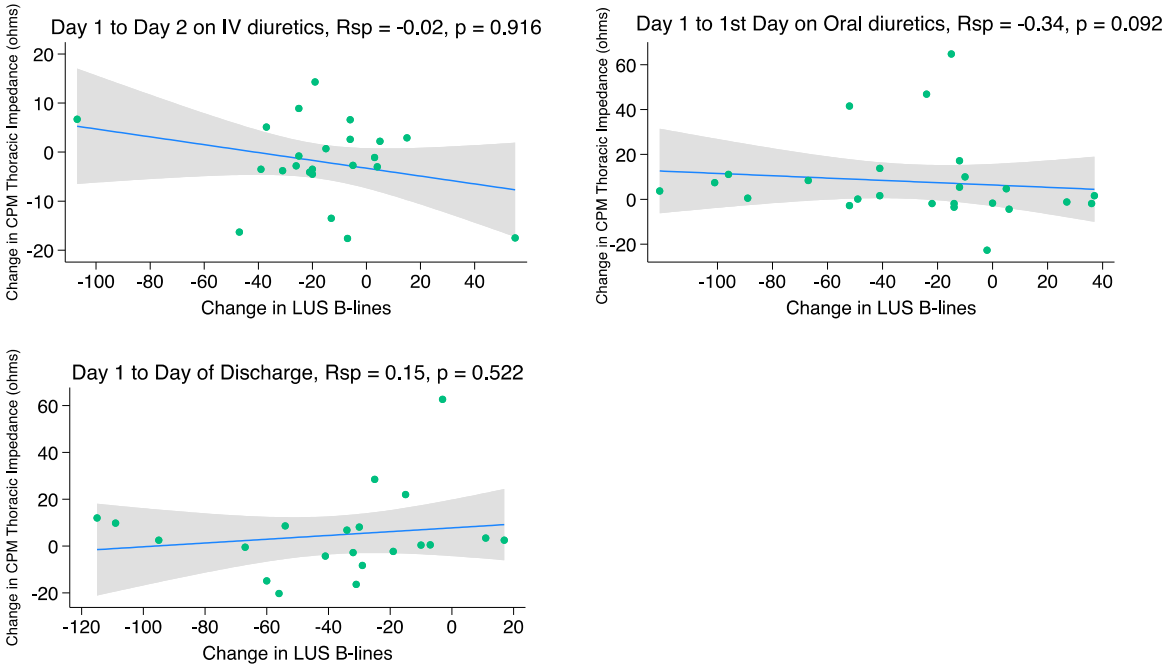


Table 7-5 Correlations between change in CPM device thoracic impedance and change in LUS B-lines per study visit

	Visit 1 to Visit 2 on IV diuretics. Change in LUS B-lines Rsp = , p Value	**Visit 1 on IV diuretics to 1st dose oral diuretics. Change in LUS B-lines Rsp = , p Value**	**Visit 1 on IV diuretics to day of discharge. Change in LUS B-lines Rsp = , p Value**
Change in CPM device thoracic impedance	-0.02, p = 0.916	-0.34, p = 0.092	0.15, p = 0.522

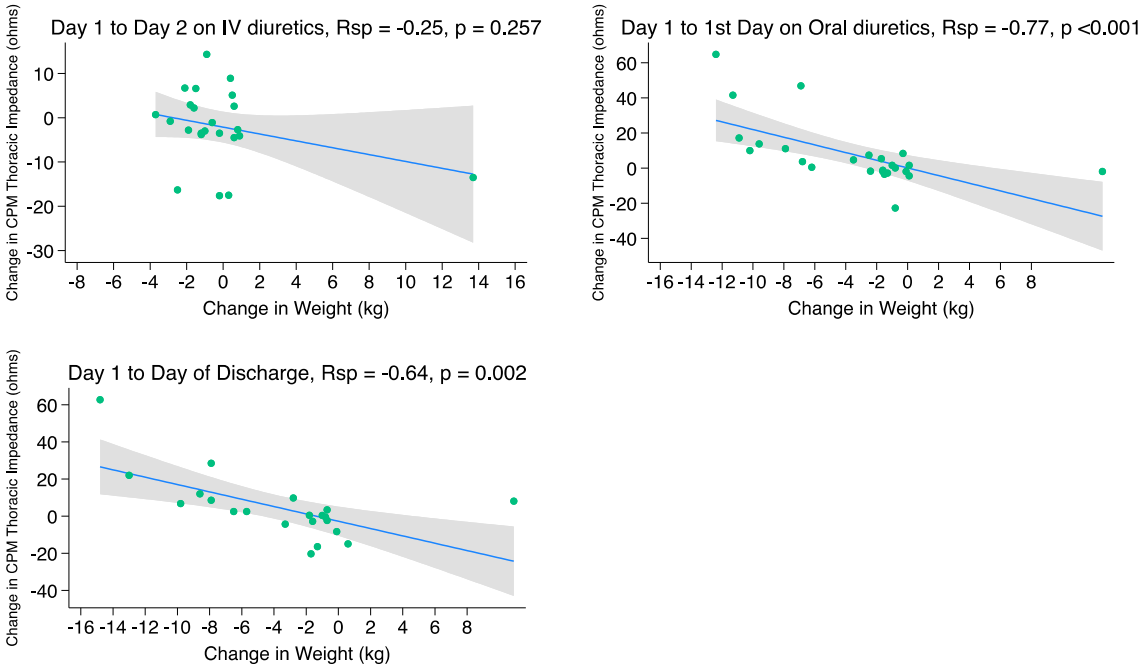
Figure 7-2 Spearman correlations between change in CPM device thoracic impedance and change in LUS B-lines per study visit



7.3.3.2 Correlation between change in CPM device thoracic impedance and change in weight

Change in device thoracic impedance and change in weight were not significantly correlated when analysed between day 1 and day 2 on IV diuretics (r_{sp} = -0.25, p = 0.257). However, the strength of the correlation increased substantially when change in both parameters was analysed between day 1 on IV diuretics and first day of oral diuretics (r_{sp} = -0.77, p <0.001) and between day 1 on IV diuretics and day of discharge (r_{sp} = -0.64, p = 0.002) (**Figure 7-3**).

Figure 7-3 Spearman correlations of change in weight and change in device thoracic impedance



7.3.3.3 Correlation between CPM device S3 and LUS B-lines and change in S3 and change in B-lines

When analysed at each corresponding study interval, CPM device S3 significantly correlated with B-lines on LUS on the day of discharge (r_{sp} = 0.48, p = 0.029) but no other study time point (**Table 7-6) (Figure 7-4)**. Change in device S3 correlated with respective change in B-lines between day 1 and day 2 of IV diuretics (r_{sp} = -0.43, p = 0.042) but at no other change interval (**Table 7-7) (Figure 7-5).**

Table 7-6 Spearman correlations between CPM device S3 and LUS B-lines per study visit

	Visit 1 on IV diuretics. LUS B-lines Rsp = , p Value	Visit 2 on IV diuretics. LUS B-lines Rsp = , p Value	1st dose oral diuretics. LUS B-lines Rsp = , p Value	Day of discharge. LUS B-lines Rsp = , p Value
CPM device S3	0.14, p = 0.514	0.34, p = 0.115	0.04, p = 0.861	0.48 p = 0.029

Figure 7-4 Spearman correlations between CPM device S3 and LUS B-lines

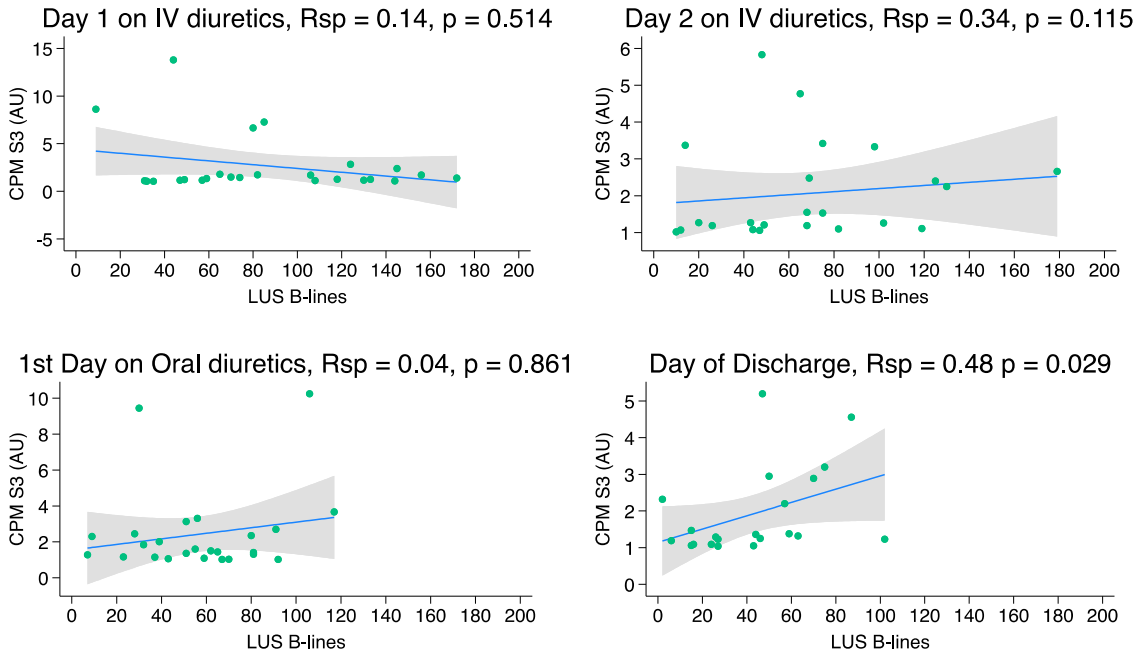
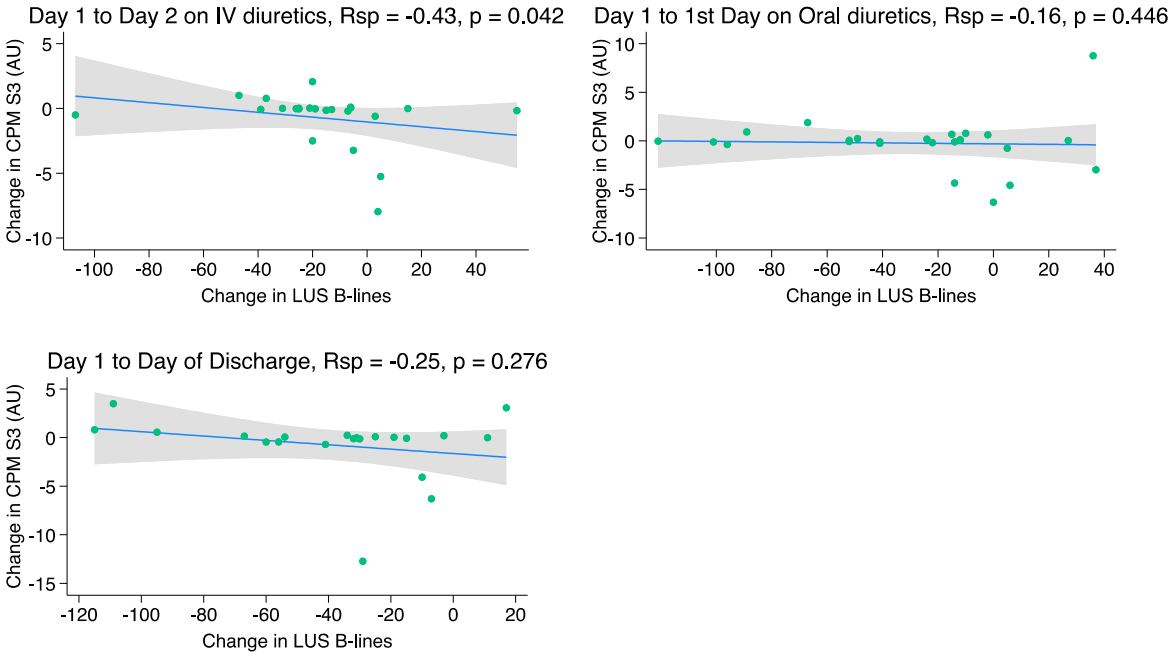


Table 7-7 Correlations between change in CPM device S3 and change in LUS B-lines per study visit

	Visit 1 to Visit 2 on IV diuretics. Change in LUS B-lines Rsp = , p Value	Visit 1 on IV diuretics to 1st dose oral diuretics. Change in LUS B-lines Rsp = , p Value	Visit 1 on IV diuretics to day of discharge. Change in LUS B-lines Rsp = , p Value
Change in CPM device S3	-0.43, p = 0.042	-0.16, p = 0.446	-0.25, p = 0.276

Figure 7-5 Spearman correlations of change in CPM device S3 and change in LUS B-lines



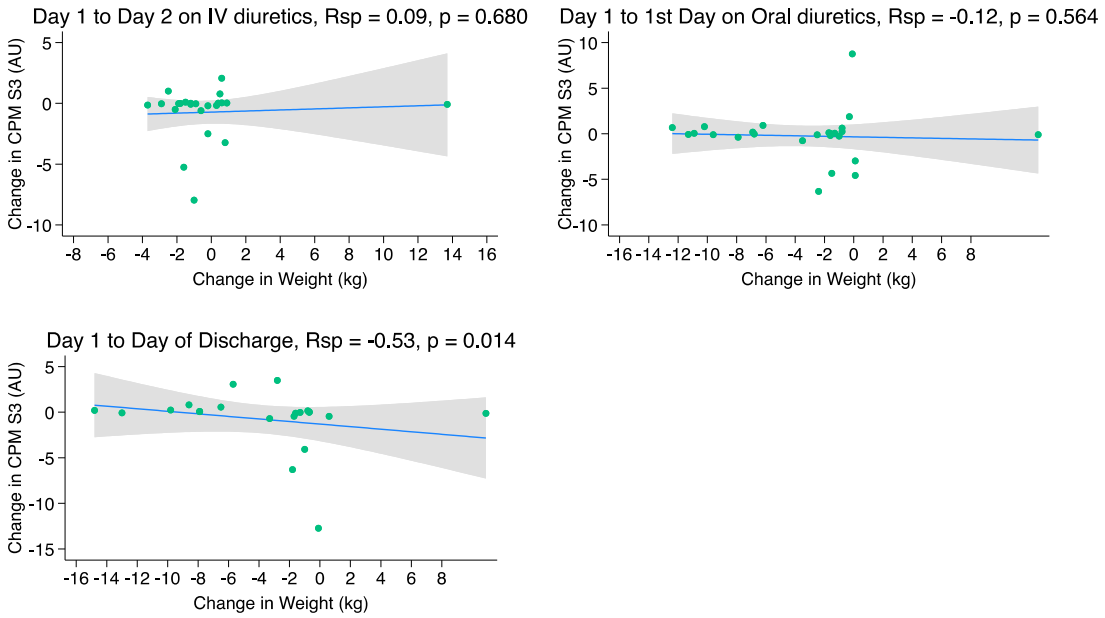
7.3.3.4 Correlation between change in CPM device S3 and change in weight

The correlation coefficient between change in device S3 and change in weight from visit 1 to visit 2 on IV diuretics was low. However, between change from visit 1 on IV diuretics to day of discharge the correlation between change in device S3 and change in weight was stronger and statistically significant (r_{sp} = -0.53, p=0.014) (**Table 7-8 and Figure 7-6**).

Table 7-8 Spearman correlations of CPM device S3 and change in weight

	Visit 1 to Visit 2 on IV diuretics. Change in Weight r_{sp} = , p Value	**Visit 1 on IV diuretics to 1st dose oral diuretics. Change in Weight r_{sp} = , p Value**	**Visit 1 on IV diuretics to day of discharge. Change in Weight r_{sp} = , p Value**
Change in CPM device S3	0.09, p = 0.680	-0.12, p = 0.564	-0.53, p = 0.014

Figure 7-6 Scatterplots of correlations between change in device S3 and change in weight



7.3.4 Secondary analyses

7.3.4.1 Correlation of CPM device tidal volume and tidal volume by spirometry

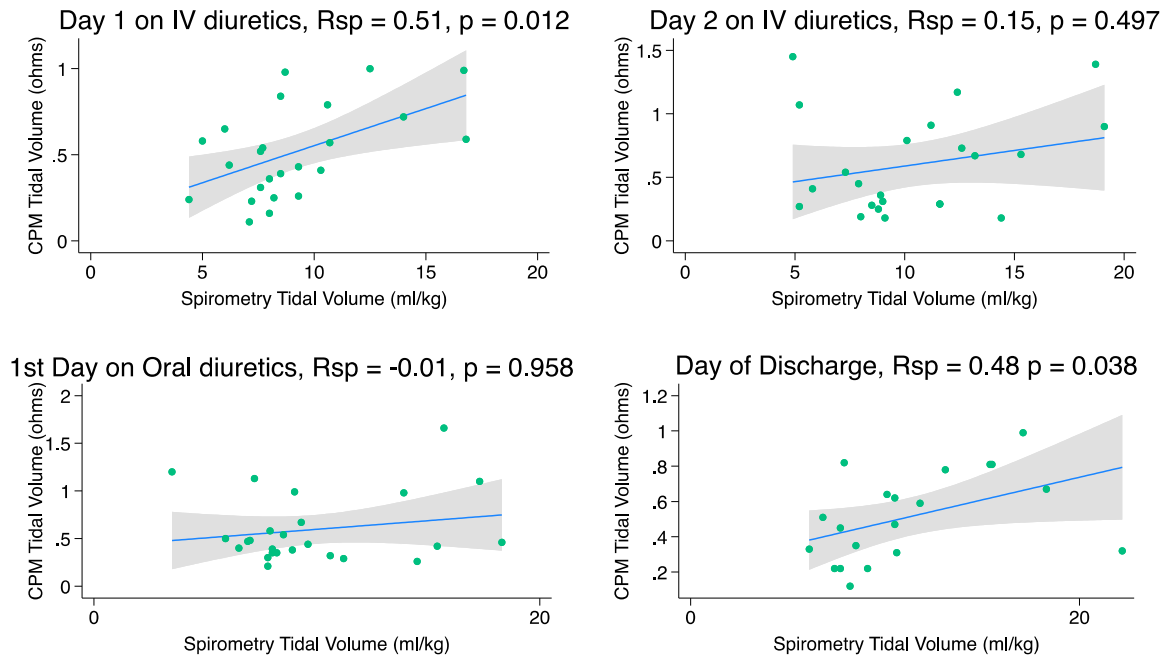
All patients had tidal volume by spirometry performed at the bedside at each study assessment. The median tidal volume on day 1 on IV diuretics was 8.5 ml/kg (7.6 – 10.6); on day 2 on IV diuretics was 9.1 ml/kg (7.9 – 12.6) (p value for difference from visit 1 = 0.031); on the first day of oral diuretics was 8.5 ml/kg (7.8 – 11.2) (p value for difference from visit 1 = 0.600); and on day of discharge was 10.1 ml/kg (7.9 – 13.1 (p value for difference from visit 1 = 0.007).

CPM device tidal volume was significantly correlated with spirometry tidal volume when analysed on day 1 of IV diuretics and day of discharge but not on day 2 of IV diuretics or day of first dose of oral diuretics (**Table 7-9**) (**Figure 7-7**).

Table 7-9 Correlations between CPM device tidal volume and tidal volume on spirometry per study visit

	Visit 1 on IV diuretics. Tidal Volume Rsp = , p Value	Visit 2 on IV diuretics. Tidal Volume Rsp = , p Value	1st dose oral diuretics. Tidal Volume Rsp = , p Value	Day of discharge. Tidal Volume Rsp = , p Value
CPM Tidal Volume	0.51, p = 0.012	0.15, p = 0.497	-0.01, p = 0.958	0.48, p = 0.033

Figure 7-7 Spearman correlations between CPM device tidal volume and tidal volume on spirometry



7.3.4.2 Correlation between change in CPM device tidal volume and change in spirometry tidal volume

Change in both tidal volume parameters across study intervals was not significantly correlated (**Table 7-10**).

Table 7-10 Correlations of change in CPM device tidal volume and spirometry tidal volume

	Visit 1 to Visit 2 on IV diuretics. Change in Spirometry Tidal Volume Rsp = , p Value	**Visit 1 on IV diuretics to 1st dose oral diuretics. Change in Spirometry Tidal Volume Rsp = , p Value**	**Visit 1 on IV diuretics to day of discharge. Change in Spirometry Tidal Volume Rsp = , p Value**
Change in CPM Tidal Volume	-0.17, p = 0.454	-0.34, p = 0.108	0.41, p = 0.084

7.3.4.3 Correlation of CPM devices measures and echocardiography

Echocardiography was performed in all patients at each study visit undertaken. Median values (IQR) are reported for the measured echocardiographic parameters per study visit in **Table 7-11**. The majority of variables did not demonstrate statistically significant changes across study assessments while patients were being decongested. LAVI, PVAT and MV inflow deceleration changed significantly between day 1 and day 2 on IV diuretics but these were not sustained until discharge.

Table 7-11 Echocardiographic values across study visits.

Parameter	Day 1 on IV diuretics	Day 2 on IV diuretics	p = *	1st day of Oral Diuretics	p = *	Day of Discharge	p = *
TR Vmax (m/s)	2.5 (1.9 – 3.0)	2.3 (1.5 – 2.9)	0.670	2.4 (1.6 – 3.1)	0.914	2.4 (1.8 – 2.6)	0.244
LAVI (ml/m^2)	52.5 (45.6 – 74.2)	48.2 (39.2 – 55.0)	0.017	50.1 (36.9 – 59.7)	0.006	50.5 (42.1 – 70.0)	0.520
E/A ratio	1.6 (1.2 – 2.2)	1.8 (1.4 – 2.7)	0.944	2.0 (1.3 – 3.0)	0.550	1.5 (1.2 – 2.3)	0.308
LV GLS (%)	-7.8 (-9.3 to -5.0)	-7.7 (-9.2 to -4.3)	0.231	-6.3 (-8.6 to -4.6)	0.780	-8.0 (-10.2 to -5.5)	0.807
LVOT VTI (cm)	17.3 (13.1 – 20.3)	18.7 (13.1 – 22.4)	0.783	17.5 (12.8 – 20.9)	0.648	20.5 (16.4 – 23.9)	0.057
PVAT (ms)	108 (85 - 128)	110 (92.5 - 149)	0.018	108.5 (90.5 – 129.5)	0.297	113 (86.5 – 124.5)	0.955
MV inflow Deceleration (ms)	174 (131 - 228)	185 (161 - 214)	0.008	175 (148 - 216)	0.154	179.5 (157 - 214)	0.513
LVEF (%)	31 (20 - 45)	28 (21 - 43)	0.772	30 (21 - 45)	0.094	33 (29 - 45)	0.148
E/e' ratio	16.7 (10.5 – 20.0)	16 (11.1 – 21.4)	0.637	13.7 (10.0 – 19.3)	0.909	13.2 (8.8 – 15.2)	0.161
IVC diameter (mm)	19.5 (16 - 26)	20 (17 - 24)	0.983	20 (17.5 – 27.0)	0.494	21.5 (15.5 – 23.5)	0.381

*p value for difference when study intervals measures were compared with measures obtained at baseline day 1 on IV diuretics

Across multiple study visits the CPM device measures (thoracic impedance, S3 and tidal volume) were weakly correlated with echocardiographic parameters.

Thoracic impedance was significantly correlated with IVC diameter (r_{sp} = 0.52, p = 0.015) on day 1 of IV diuretics, with LAVI on the second day of IV diuretics (r_{sp} = -0.54, p = 0.010), with LVOT VTI on the first day of oral diuretics (r_{sp} = 0.48, p = 0.019) and with TR Vmax (r_{sp} = -0.52, p = 0.017) on day of discharge. (**Table 7-12**)

On the first day of IV diuretics, the CPM device S3 and E/e' ratio were significantly correlated (r_{sp} = 0.44, p = 0.030). Device S3 and MV inflow deceleration were inversely correlated on the second day of IV diuretics (r_{sp} = -0.43, p = 0.043). Lastly, in the analysis of parameters obtained on the day of discharge, device S3 and E/A ratio (r_{sp} = 0.66, p = 0.023) and device S3 and LAVI (r_{sp} = 0.52, p = 0.025) were significantly correlated **(Table 7-13)**.

When device tidal volume was analysed, only LVOT VTI on day 1 of IV diuretics (r_{sp} = -0.47, p = 0.025) and LAVI (r_{sp} = -0.59, p = 0.008) on day of discharge were significantly correlated.

Table 7-12 Correlation of CPM device thoracic impedance and echocardiographic measures across study assessments

Parameter	Visit 1 on IV diuretics. Thoracic Impedance Rsp = , p Value	Visit 2 on IV diuretics. Thoracic Impedance Rsp = , p Value	1st dose oral diuretics. Thoracic Impedance Rsp = , p Value	Day of discharge. Thoracic Impedance Rsp = , p Value
LAVI (ml/m^2)	-0.38, p = 0.058	-0.54, p = 0.010	-0.32, p = 0.121	-0.41, p = 0.080
PVAT (ms)	0.13, p = 0.530	0.18, p = 0.407	-0.03, p = 0.885	0.14, p = 0.564
LVEF (%)	-0.07, p = 0.745	0.06, p = 0.799	-0.08, p = 0.699	-0.05, p = 0.821
TR Vmax (m/s)	-0.07, p = 0.723	-0.32, p = 0.130	-0.14, p = 0.503	-0.52, p = 0.017
MV inflow deceleration (ms)	-0.05, p = 0.792	0.08, p = 0.728	0.09, p = 0.658	0.05, p = 0.839
LVOT VTI (cm)	0.13, p = 0.548	0.20, p = 0.361	0.48, p = 0.019	0.31, p = 0.174
E/A ratio	-0.05, p = 0.848	-0.15, p = 0.581	-0.45, p = 0.082	-0.37, p = 0.231
E/e' ratio	0.14, p = 0.491	0.07, p = 0.740	0.12, p = 0.575	-0.05, p = 0.846
IVC diameter (mm)	-0.52, p = 0.015	-0.34, p = 0.126	-0.21, p = 0.328	-0.43, p = 0.060
LV GLS (%)	0.11, p = 0.638	-0.15, p = 0.539	0.17, p = 0.479	0.27, p = 0.369

Table 7-13 Correlation of CPM device S3 and echocardiographic measures across study assessments

Parameter	Visit 1 on IV diuretics. CPM device S3 Rsp = , p Value	Visit 2 on IV diuretics. CPM device S3 Rsp = , p Value	1st dose oral diuretics. CPM device S3 Rsp = , p Value	Day of discharge. CPM device S3 Rsp = , p Value
LAVI (ml/m^2)	-0.13, p = 0.531	-0.20, p = 0.367	-0.13, p = 0.530	0.52, p = 0.025
PVAT (ms)	-0.08, p = 0.707	-0.17, p = 0.434	-0.22, p = 0.297	-0.39, p = 0.092
LVEF (%)	0.04, p = 0.847	0.004, p = 0.985	0.11, p = 0.596	0.23, p = 0.299
TR Vmax (m/s)	0.06, p = 0.777	0.23, p = 0.279	0.09, p = 0.653	0.20, p = 0.374
MV inflow deceleration (ms)	-0.24, p = 0.243	-0.43, p = 0.043	-0.30, p = 0.141	-0.18, p = 0.433
LVOT VTI (cm)	-0.12, p = 0.588	-0.27, p = 0.214	-0.17, p = 0.414	0.09, p = 0.702
E/A ratio	0.44, p = 0.088	0.44, p = 0.098	0.28, p = 0.290	0.66, p = 0.023
E/e' ratio	0.44, p = 0.030	0.29, p = 0.178	0.11, p = 0.615	0.24, p = 0.309
IVC diameter (mm)	-0.09, p = 0.699	-0.10, p = 0.677	-0.03, p = 0.872	0.39, p = 0.087
LV GLS (%)	0.03, p = 0.904	0.08, p = 0.742	-0.07, p = 0.738	0.13, p = 0.663

7.3.4.4 Correlations between change in CPM device measures and change in echocardiography

Correlation between change in both device measures and echocardiography was also poor. When change between day 1 and 2 of IV diuretics was analysed, thoracic impedance and PVAT (r_{sp} = 0.68, p < 0.001) and MV inflow deceleration (r_{sp} = 0.45, p = 0.033) were significantly correlated. Change between first day of IV diuretics and first of oral diuretics in CPM device tidal volume was correlated with change in E/e' ratio at the same time point (r_{sp} = 0.57, p = 0.005). Change in CPM device tidal volume was not correlated with any other echocardiographic parameters. Lastly, device S3 was not correlated with change in any echocardiographic parameters.

7.3.4.5 Clinical examination findings across study assessments

All 25 patients were examined at each study interval. On study day 1 on IV diuretics, 22 of 25 (88.0%) patients had an elevated JVP (>4cm). Among these 22 patients, the median measured JVP was 10 cm (8 - 12). At subsequent assessments, 16 patients (64%) had a visible JVP on second day of IV diuretics (p value for difference with baseline = 0.046); 13 (52%) had an elevated JVP on the day of first oral diuretic (p value for difference with baseline = 0.004); and 5 people had an elevated JVP on discharge (20%) (p value for difference with baseline < 0.001). People who had an elevated JVP at the first study assessment and who did not have a visible JVP on discharge, experienced less weight loss during decongestion than people who continued to have an elevated JVP at discharge [-1kg (-1.7 to -0.7 versus -8.6kg (-9.8 to -7.9), p = 0.007]. Change in JVP elevation did not correlate significantly with change in weight at any of the study intervals.

6 of 25 (24%) had an audible clinical S3 on examination at study baseline day 1 on IV diuretics. A clinical S3 remained audible in 5 (20%) people on day 2, (p = 0.564), in 1 (4%) person on the day of switching to oral diuretics (p = 0.059) and was not apparent on examining any patient on the day of discharge (p = 0.025).

Pulmonary rales were audible in 19 of 25 people (76%) examination at study baseline day 1 on IV diuretics. When compared to baseline assessment, rales remained audible in most people (18 of 25, 72%) on day 2, (p = 0.564), in 14 (56%) people on the day of switching to oral diuretics (p = 0.059) and 12 patients (48%) on the day of discharge (p = 0.206). There was no difference in change in weight from baseline to discharge between people whose rales resolved during the admission and people who continued to have rales at the final study visit [-2.8kg (-8.6 to -0.7) versus -1.8kg (-7.9 to -0.8), p = 0.750].

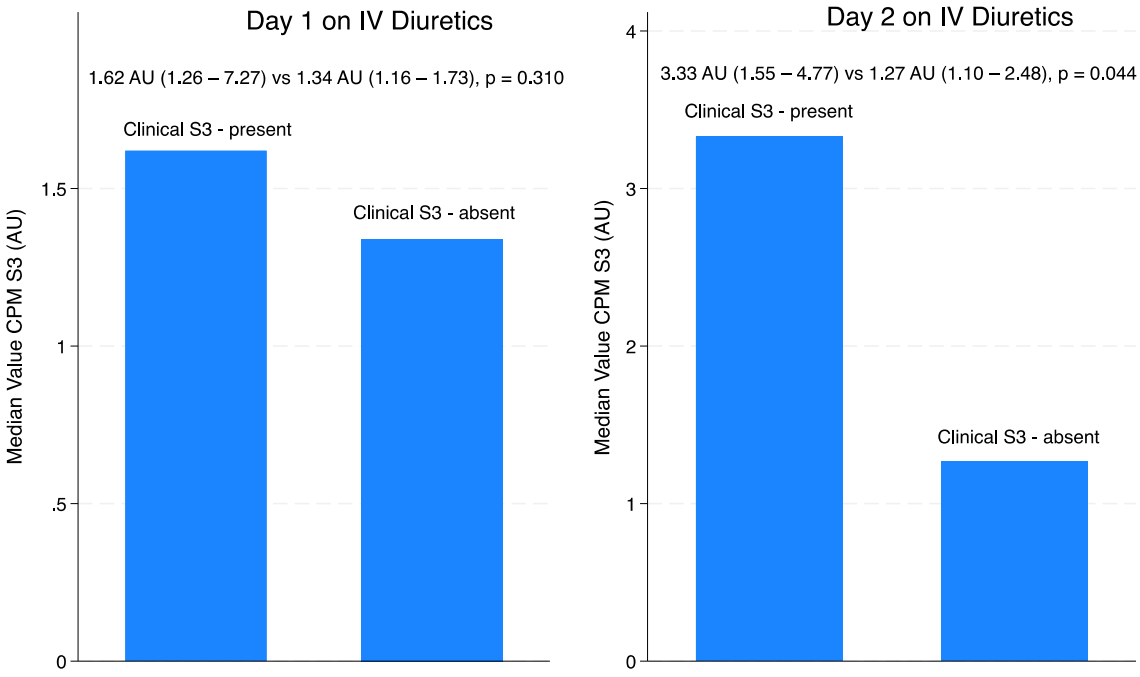
Peripheral oedema was apparent on examination in 22 people (88%) on day 1 of IV diuretics, Compared with this baseline assessment, oedema remained evident in 20 people (80%) on day 2 (p = 0.317), 18 patients (72%) on first day of oral diuretics (p = 0.046) and 7 people (28%) (p < 0.001) by discharge. No difference in total admission weight loss was observed between people whose oedema resolved at the point of discharge and those who had some oedema remaining [-2.8kg (-7.9 to -1.6) to -5.7kg (-9.8 to -0.7), p = 1.000].

7.3.4.6 Correlation between clinical examination and CPM device measures

In people who had an audible clinical S3, compared with people without a clinical S3, the median CPM device S3 value was numerically greater [1.62 AU (1.26 – 7.27) vs 1.34 AU (1.16 – 1.73), p = 0.310] on day 1 IV diuretics, a difference that reached statistical significance on day 2 of IV diuretics [3.33 AU (1.55 – 4.77) vs 1.27 AU (1.10 – 2.48), p =

0.044]. By first day of oral diuretics, only one patient continued to have an audible S3 and there was no differences between groups in CPM device S3 (1.0 AU (1.0 – 1.0) vs 1.6 AU (1.2 – 2.6)) (**Figure 7-8**).

Figure 7-8 Bar charts comparing the median CPM S3 energy according to the presence or absence of a clinical third heart sound.



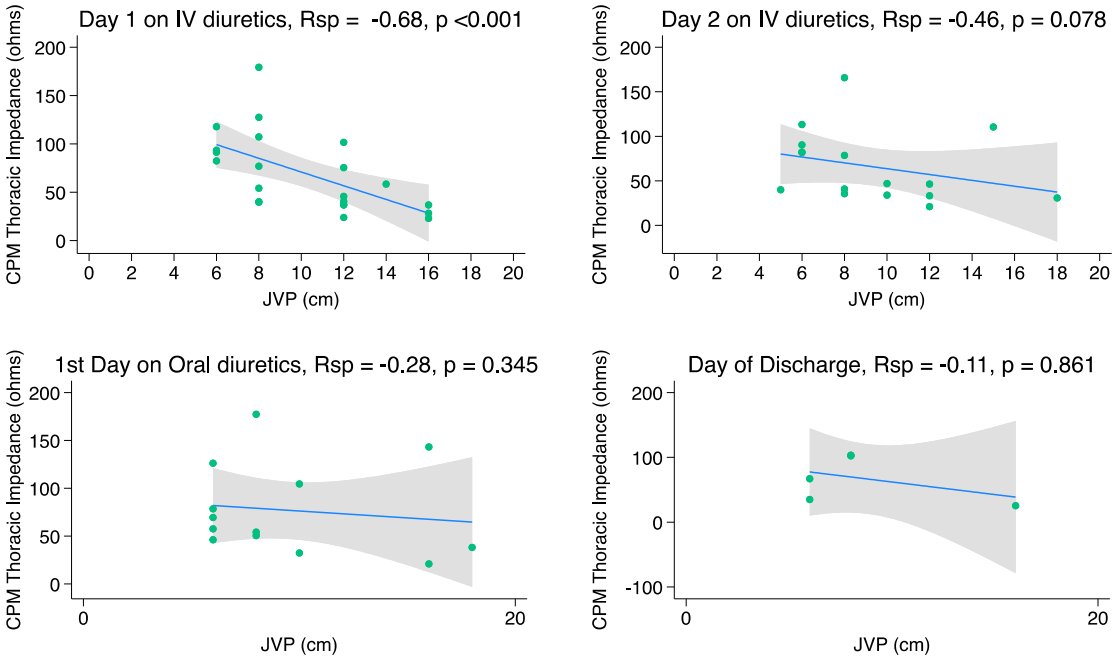
There was no difference between CPM device thoracic impedance or CPM device tidal volume in patients who did or did not have an audible S3 on examination at any study visit. People who had audible pulmonary rales on examination compared with those without rales, had no difference between groups in CPM device thoracic impedance or median CPM S3 across study assessments. On day 1 of IV diuretics, CPM device tidal volume was higher in patients without rales [0.4 ohms (0.3 – 0.6) versus 0.8 ohms (0.7 – 1.0), p = 0.020] who had rales. However, as the numbers of people without rales reduced across study assessments,

there was no apparent difference in tidal volume between groups from day 2 on IV diuretics onwards.

Among people who had clinical evidence of peripheral oedema, compared with people with no evidence of oedema, CPM device S3 was higher on both day 1 [1.5 AU (1.2 – 2.4) vs 1.2 AU (1.1 – 1.2), p = 0.049] and day 2 [1.54 AU (1.2 – 3.0) vs 1.1 AU (1.0 – 1.2), p = 0.045] of IV diuretics. On later study assessments a similar numerical difference was present but was not statistically significant. While CPM device thoracic impedance was numerically lower in people with oedema compared to people without oedema over the initial 3 study assessments, this difference only reached statistical significance on the day of discharge (62.0 ohms (35.0 – 66.0) vs 91.0 ohms (53.6 – 103.4), p = 0.025). There was no difference in device tidal volume between people who had peripheral oedema compared with people who did not at any study time point.

Among people who had a visible JVP there was no significant correlation between visible level of JVP elevation (cm) and device tidal volume or device S3 at any study assessment point. Device thoracic impedance was strongly and inversely correlated with JVP elevation on day 1 of IV diuretics (r_{sp} = -0.68, p <0.001). The strength of the correlation diminished across study visits as the numbers of patients with a visible JVP reduced [Day 2 on IV diuretics, n = 16: r_{sp} = -0.46, p = 0.077; first day of oral diuretics, n = 13: r_{sp} = -0.28, p = 0.344; day of discharge, n = 5: r_{sp} = -0.11, p = 0.861] **(Figure 7-9)**. Change in JVP elevation across different study assessments did not correlate significantly with change in any of the device parameters.

Figure 7-9 Spearman correlations of JVP elevation (cm) and device thoracic impedance



7.3.4.7 Correlation of CPM device measures and clinical symptoms

Overall, there was a steady increase in the proportions of patients experiencing an improvement in symptoms, as recorded by changes in NYHA functional class, the EVEREST dyspnoea and total congestion scores and presence or absence of either bendopnoea or orthopnoea from day 1 on IV diuretics through to discharge (**Table 7-14**).

Table 7-14 Proportions of patients experiencing symptoms according to study visit assessment

	Visit 1 on IV diuretics. N = 25	Visit 2 on IV diuretics. N = 23	1st dose oral diuretics. N = 25	Day of discharge. N = 21	p = *
NYHA class (%)					<0.001
1	-	1 (4.3)	3 (12)	8 (38.1)	
2	7 (28.0)	10 (43.5)	15 (60)	11 (52.4)	
3	10 (40.0)	4 (17.4)	5 (20)	1 (4.8)	
4	8 (32.0)	8 (34.8)	2 (8)	1 (4.8)	
EVEREST dyspnoea score					<0.001
None	-	2 (8.7)	4 (16.0)	7 (33.3)	
Seldom	6 (24.0)	8 (34.9)	14 (56.0)	11 (52.4)	
Frequent	10 (40.0)	4 (17.4)	3 (12.0)	2 (9.5)	
Constant	9 (36.0)	9 (39.1)	4 (16.0)	1 (4.8)	
Total EVEREST congestion score	10 (6 - 12)	9 (5 - 12)	6 (4 - 8)	3 (1 - 4)	<0.001
Bendopnea (%)					0.031
Yes	11 (44.0)	9 (39.1)	4 (16)	1 (4.8)	
No	14 (56.0)	14 (60.9)	21 (84)	20 (95.2)	
Orthopnoea (%)					0.005
Yes	13 (52)	12 (52.2)	9 (36)	3 (14.3)	
No	12 (48)	11 (47.8)	16 (64)	18 (85.7)	

*P value for difference between baseline day 1 on IV diuretics compared with day of discharge

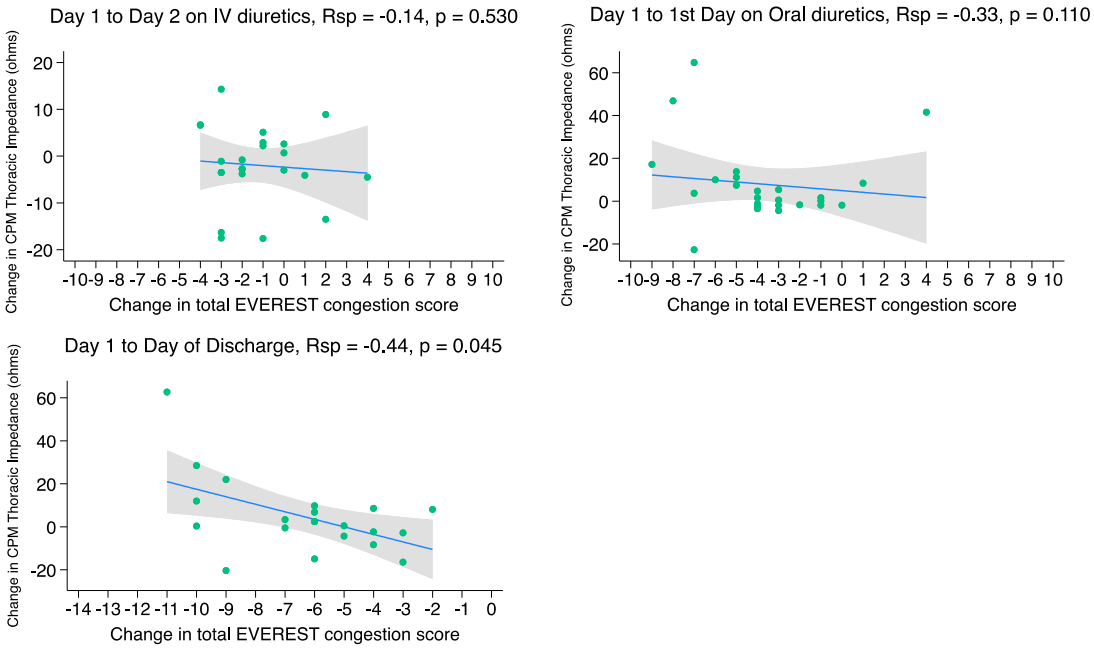
7.3.4.8 Correlation between clinical symptoms and CPM device measurements

There were no differences in the CPM device measurements between people who experienced, or did not experience, dyspnoea on the EVEREST scale, bendopnoea or according to NYHA functional class at any given study interval. People who had orthopnoea on the first day of IV diuretics had a lower CPM device S3 than those who did not [1.2 AU (1.1 – 1.5) vs 1.7 AU (1.3 – 2.6), p = 0.044], a difference that did not persist on analysis of the following three study assessments. There were no significant correlations between total EVEREST score and CPM device S3, tidal volume or thoracic impedance.

7.3.4.9 Correlation between change in symptoms and change in CPM device measures

Change in total EVEREST congestion score was poorly correlated with change in device thoracic impedance until change between day of first IV diuretics and day of discharge was analysed (r_{sp} = -0.44, p = 0.045) (**Figure 7-10**).

Figure 7-10 Spearman correlations of change in total EVEREST congestion score and change in thoracic impedance



Change in total EVEREST congestion score was not correlated significantly with change in CPM tidal volume or device S3.

People who self-reported an improvement in breathlessness on the EVEREST dyspnoea scale between day 1 of IV diuretics and day of discharge had no difference in thoracic impedance, device S3 or tidal volume compared with people who remained at the same point or had an increase in dyspnoea. This was also the case for people with a reduction in NYHA class, bendopnoea and orthopnoea from day 1 to day of discharge compared with people who had either no change or an increase in these symptoms.

7.3.4.10 Correlation between CPM device measurements and biomarkers of congestion

7.3.4.10.1 NT-proBNP

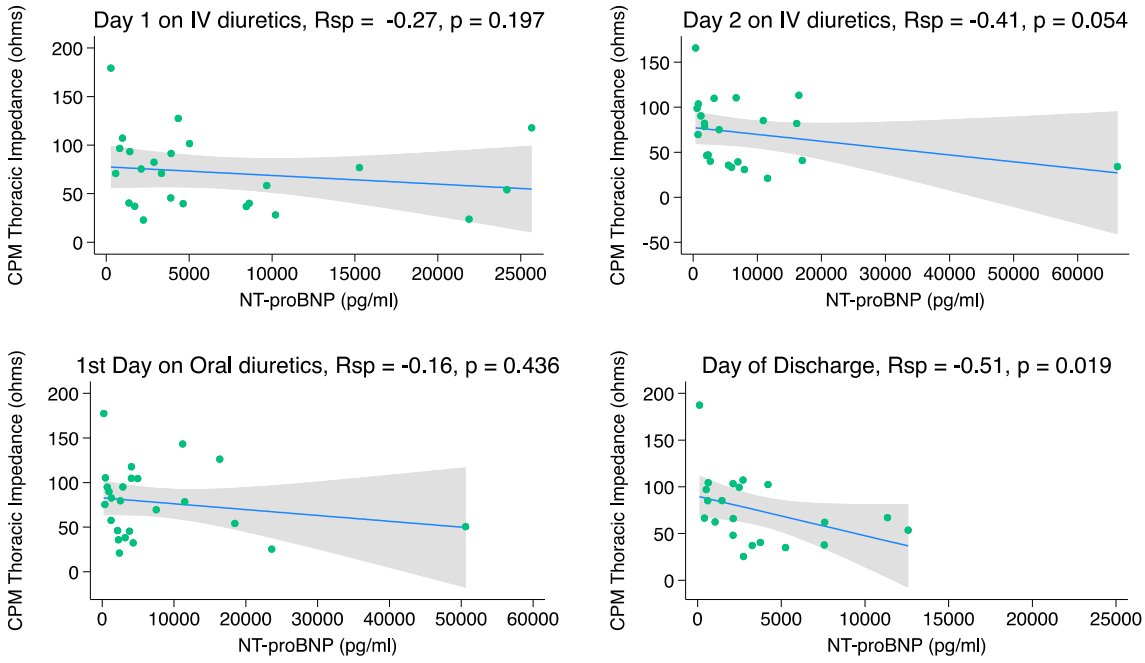
One patient with poor IV access, missed a blood sample on the day of an assessment. Otherwise, there were no missing biomarker (NT-proBNP or MR-proANP) data at any study time point. The median NT-proBNP across study visits was 3899 pg/ml (1567 - 9150) on day 1 of IV diuretics; 4046 pg/ml (1764 - 10938) (p for difference with baseline = 0.372), on day 2; 3205pg/ml (1285 - 7527) (p for difference with baseline = 0.024) on first day of oral diuretics; and 2486 pg/ml (p value for difference with baseline = 0.007) on day of discharge. Change in NT-proBNP was not correlated significantly with change in weight.

NT-proBNP was correlated significantly with thoracic impedance on the day of discharge only (**Figure 7-11**). CPM device S3 or tidal volume did not correlate significantly with NT-proBNP (**Table 7-15**). Change in NT-proBNP was not significantly correlated with change in any device parameter at any study time point.

Table 7-15 Spearman correlations between CPM device measures and NT-proBNP study visit

	Visit 1 on IV diuretics. NT-proBNP Rsp = , p Value	Visit 2 on IV diuretics. NT-proBNP Rsp = , p Value	1st dose oral diuretics. NT-proBNP Rsp = , p Value	Day of discharge. NT-proBNP Rsp = , p Value
Device Thoracic Impedance	-0.27, p = 0.197	-0.41, p = 0.054	-0.16, p = 0.436	-0.51, p = 0.019
Device S3	-0.11, p = 0.619	0.05, p = 0.820	0.09, p = 0.663	0.19, p = 0.415
Device Tidal Volume	0.001, p = 0.996	-0.36, p = 0.093	-0.06, p = 0.763	-0.003, p = 0.987

Figure 7-11 Spearman correlations between CPM device thoracic impedance and NT-proBNP



7.3.4.10.2 MR-proANP

The median MR-proANP across study visits was 487 pmol/L (367 - 595) on day 1 of IV diuretics; 493 pmol/L (313 – 601) (p for difference with baseline = 0.987) on day 2; 401 pmol/L (313 - 702) (p for difference with baseline = 0.046) on first day of oral diuretics; and 406 pmol/L (255 - 532) (p value for difference with baseline = 0.010) on day of discharge. Change in MR-proANP was not correlated significantly with change in weight.

MR-proANP did not correlate significantly with any device parameter, although there appeared to be a relationship between thoracic impedance and MR-proANP at the point of discharge (**Table 7-16**). Analysed between day 1 and day 2 of IV diuretics, change in MR-proANP was correlated with change in CPM device S3 (r_{sp} = 0.46, p = 0.031) and change in tidal volume (r_{sp} = -0.53, p = 0.015) but not for change between baseline day 1 and any other subsequent time point. Change in thoracic impedance was not significantly correlated with change in MR-proANP.

Table 7-16 Spearman correlations (Rsp) between CPM device measures and MR-proANP per study visit

	Visit 1 on IV diuretics. MR-proANP Rsp = , p Value	Visit 2 on IV diuretics. MR-proANP Rsp = , p Value	1st dose oral diuretics. MR-proANP Rsp = , p Value	Day of discharge. MR-proANP Rsp = , p Value
Device Thoracic Impedance	-0.39, p = 0.063	-0.38, p = 0.077	-0.11, p = 0.611	-0.42, p = 0.056
Device S3	-0.30, p = 0.159	-0.008, p = 0.971	0.07, p = 0.734	0.28, p = 0.214
Device Tidal Volume	-0.28, p = 0.199	-0.35, p = 0.099	-0.07, p = 0.739	-0.09, p = 0.695

7.3.4.10.3 Haematocrit

Haematocrit was collected as part of routine care and was missing in 2 patients on day 1, 3 patients on day 2, 3 patients on first day of oral diuretics and on the day of discharge. The median haematocrit was 0.39 L/L (0.31 – 0.44) on day 1 of IV diuretics, 0.40 L/L (0.40 – 0.43) on day 2 of IV diuretics, 0.38 (0.35 – 0.43) on the first day of oral diuretics and 0.38 (0.32 – 0.41) on the day of discharge. There was no statistical difference between baseline haematocrit and haematocrit collected at any subsequent study visits. Change in haematocrit was not correlated significantly with change in weight.

Haematocrit collected on day 1 of IV diuretics was correlated with device tidal volume but not with device S3 or thoracic impedance at any time point. Change in haematocrit was correlated with change in thoracic impedance between day 1 of IV diuretics and day of first

oral diuretics (r_{sp} = 0.53, p = 0.017) but not with change in device S3 or tidal volume at any time point (**Table 7-17**).

Table 7-17 Spearman correlations (Rsp) between haematocrit and CPM device measures per study visit

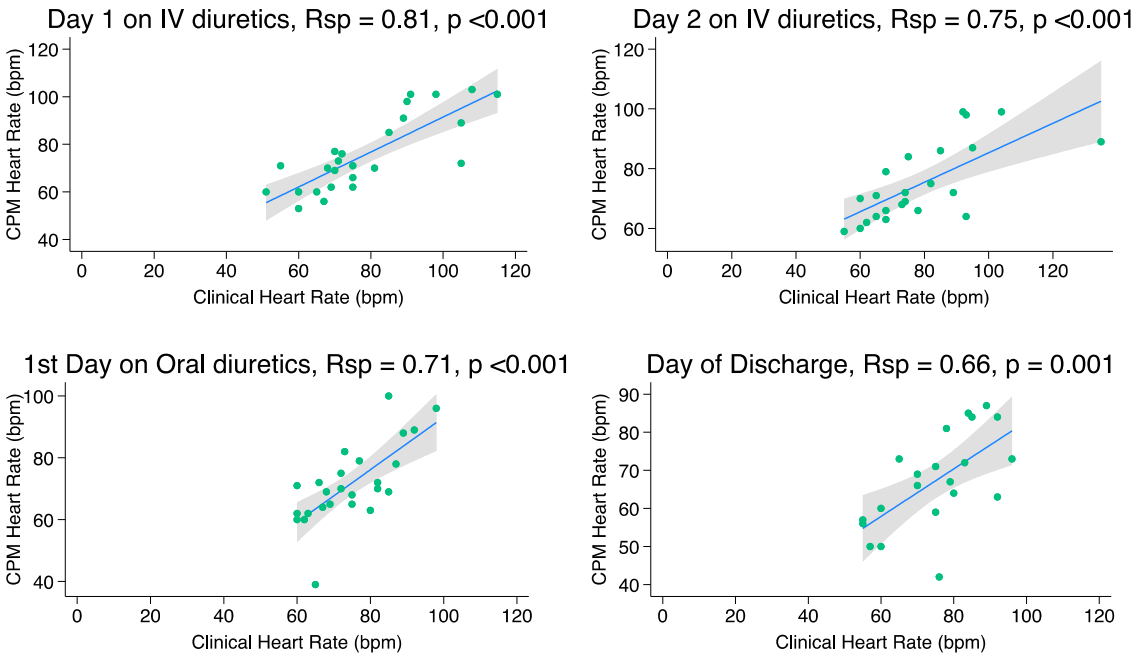
	Visit 1 on IV diuretics. Haematocrit Rsp = , p Value	**Visit 2 on IV diuretics. Haematocrit Rsp = , p Value**	**1st dose oral diuretics. Haematocrit Rsp = , p Value**	**Day of discharge. Haematocrit Rsp = , p Value**
Device Thoracic Impedance	0.26, p = 0.230	-0.03, p = 0.888	0.097, p = 0.666	-0.08, p = 0.761
Device S3	-0.30, p = 0.159	-0.008, p = 0.971	0.07, p = 0.734	0.28, p = 0.214
Device Tidal Volume	0.47, p = 0.029	0.17, p = 0.439	0.27, p = 0.224	0.19, p = 0.450

7.3.4.11 Correlation between surface ECG and CPM device measurements

The median heart rate on clinical examination at baseline day 1 on IV diuretics was 75 bpm (68 - 90) and was 74 (65 - 92), 73 (66 - 82) and 76 (65 - 84) on the subsequent 3 study visits with no difference observed between intervals. 23 of 25 (92%) people had a baseline ECG performed as part of standard care. On day 1 of IV diuretics, clinical heart rate and device heart rate were strongly correlated (r_{sp} = 0.81, p <0.001). On serial measures, CPM device heart rate and clinical heart rate remained significantly correlated on day 2 on IV diuretics (n

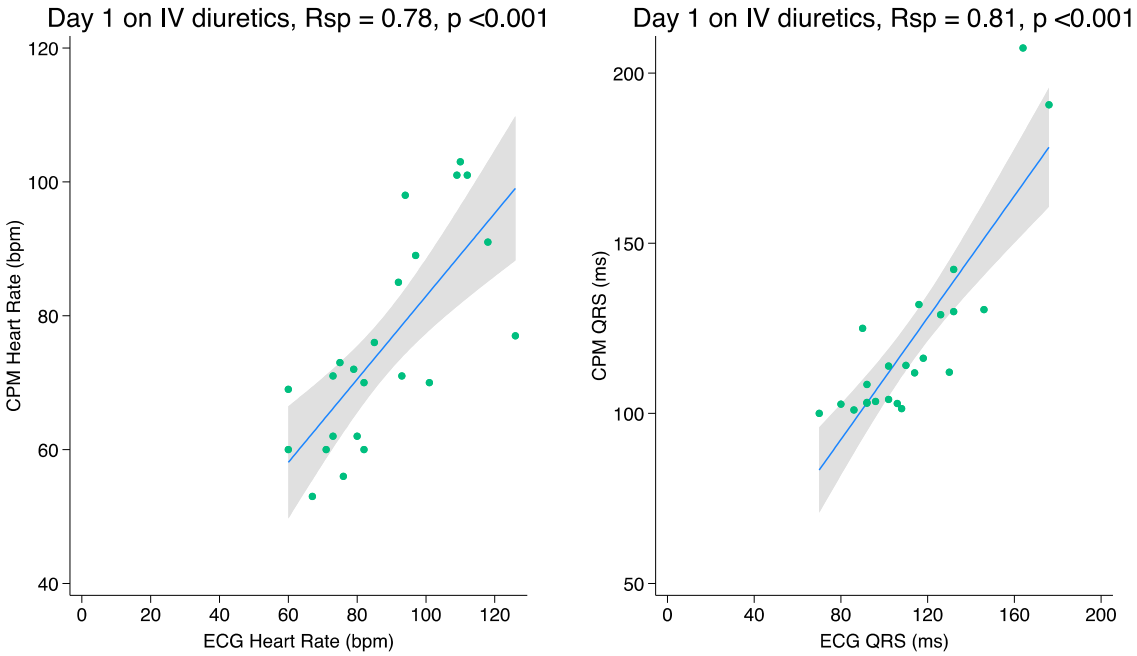
= 23, r_{sp} = 0.75, p < 0.001), on day of first dose of oral diuretics (n = 25, r_{sp} = 0.71, p < 0.001) and day of discharge (r_{sp} = 0.66, p = 0.001) (**Figure 7-12**).

Figure 7-12 Spearman correlations between clinical heart rate and CPM device heart rate by study visit



At baseline day 1 on IV diuretics, CPM device heart rate and heart rate on ECG were also strongly correlated (r_{sp} = 0.78, p <0.001) (**Figure 7-13**). The median ECG QRS duration was 108 milliseconds (92 - 130). ECG QRS and CPM device QRS were strongly correlated (r_{sp} = 0.81, p < 0.001) (**Figure 7-13**).

Figure 7-13 Spearman correlations between CPM device ECG and surface ECG parameters



A high level of agreement was demonstrated between the CPM device Rhythm algorithm and clinical pulse irregularity (**Table 7-18**).

Table 7-18 Relation between the CPM device Rhythm algorithm and pulse irregularity on clinical examination

Parameter	CPM Device	Kappa	p =
Pulse – irregular, Visit 1	**Rhythm, Visit 1**	**0.636**	**<0.001**
Pulse – irregular, Visit 2	**Rhythm, Visit 2**	**0.904**	**<0.001**
Pulse – irregular, Visit 3	**Rhythm, Visit 3**	**0.659**	**<0.001**
Pulse – irregular, Visit 4	**Rhythm, Visit 4**	**0.894**	**<0.001**

7.3.4.12 Missed study visits and patient withdrawal

5 patients missed a single study visit. 1 of these patients had a sudden death while an inpatient between study visits 3 and 4 and so did not undergo the final day of discharge assessment. 1 patient was withdrawn from the study due to receiving palliative care and it

was clear they would not be discharged from hospital (as required by the protocol for visit 4). 1 patient was withdrawn from the study as due to unforeseen circumstances I was unable to conduct a study visit on the day they were discharged and there was no other investigator to cover a study assessment. 2 patients were switched directly to oral diuretics within 24 hours of enrolling in the study and therefore their second study assessment was recorded as visit 3. Lastly, 1 patient was still in the study, with a long admission and remained an inpatient when the study finished meaning they did not have a study visit 4 (protocol scheduled for day of discharge).

7.3.4.13 Adverse Events

There were no device related adverse events in this study cohort, including no evidence of device-device interaction in any patients with an implanted cardiac device.

7.3.4.14 Device Deficiencies

3 device deficiencies occurred in 2 patients during the study as detailed below in **Table 7-19**. There was no impact on device data collection.

Table 7-19 CPM wearable device deficiencies in Cohort C of the CONGEST-HF study.

Date	Device ID	Patient ID	Type of Incident	When deficiency was identified	Action taken
10/06/2022		02040	Device malfunction – No connection between device and mobile app.	During use	Device reset by the investigator and connection established with study visit device readings performed as standard.
05/07/2022	ADI11640-4	02047	Device malfunction – loss of auscultation waveform	During use	No action taken – valid readings were achieved after ensuring firm adequate contact between device adhesive and chest skin
06/07/2022	ADI11640-4	02047	Device malfunction – loss of auscultation and thoracic impedance waveforms	During use	Device removed from study and a new device (ADI11651-2) was paired to the patient and the study visit readings completed. Device returned to Analog Devices Inc.

7.4 Discussion

In this study I recruited 25 patients who were admitted to hospital with a decompensation in HF. These people were enrolled irrespective of HF aetiology or LVEF provided they were sufficiently congested to require treatment with IV diuretics. People enrolled in this study were specifically targeted to represent the broader population of patients living with HF, the intended-use group for the CPM wearable device. The mean age in this cohort was 72.8 ± 12.5 years and was predominantly male (72%). This was consistent with the age rather than the sex demographic of the England and Wales National HF Audit 2021 in which the mean age was 77.7 years and 57.1% were male[3]. The study cohort age was also in keeping with or slightly older than those reported in several international registries of patients hospitalized with HF, and compared to which there remained a difference in the proportions of males to females. These include the GWTG-HF [mean age 72.6 years ± 14.2, 51% male][6], REPORT-HF [67.0 years (57.0 - 77.0), 61.3% male][319] and ESC-EORP-HFA [mean age 69.0 ± 12.9 years, 62.9% male][320] registries. With the exception of GUIDE-HF [median age 70.5 (64 – 76.5), 62.5% males][54], most trials of wearable or implanted devices or acute heart failure therapies enrolled substantially younger patients than this study's cohort with similar or fewer numbers of female participants; CHAMPION [61.5 years ± 13, 72.5% male], LAPTOP-HF [62 ± 12 years, 75% male] and LINK-HF [mean age 68.4 ± 10.2, 98% male][87], DOSE [mean age 66 years, 73% male][321]. The discrepancy between trial cohorts and real-world datasets is well recognised, with males and younger people often over-represented in the former. While this study reflected the older demographic of contemporary populations of patients admitted with HF, there were fewer women than might have been otherwise anticipated. During screening for this study, women were as likely to consent to participation as men if approached and the higher proportion of male patients reflects the available pool of eligible

patients during the 6 months of active recruitment. Similarly, the study cohort were almost entirely White in ethnicity (92%), likely accounted for by the demographic of people living with HF in Glasgow.

Infections, particularly respiratory, have been reported to be frequent precipitating causes of HF decompensation[6,322]. In this study, both pneumonia and COVID infection were exclusion criteria due to the risk of transmission and the confounding effect these conditions can have on LUS in particular. I did not specifically record the main driver of worsening HF in this study, but the baseline characteristics are in keeping with a high-risk population. Just over half (52%) had been previously hospitalized, and in approximately half of these people (46%) the previous hospitalization had been within the prior 6 months. On average patients had severely impaired LV systolic function (mean LVEF 31% ± 15), a markedly elevated median NT-proBNP [3899 (1567 - 9151)] and moderately impaired renal function [eGFR 49 mL/min/1.73m^2], with each of these parameters consistent with what would be anticipated in a high-risk HF cohort. In the DOSE trial, the mean LVEF was higher (35%), the mean creatinine slightly lower 132 mmol/L (compared with 138 mmol/L in this present study) and the median NT-proBNP higher at 7439 pg/ml, the latter being potentially explained by higher proportions of people with atrial fibrillation (53% vs 48%) and the earlier enrolment of patients in DOSE[321]. In ASCEND-HF, the median NT-proBNP was similar [4508 (2076 - 9174)], and in the present study NT-proBNP was considerably higher than patients enrolled in the wearable device study LINK-HF who were recruited during a hospitalization for HF [1539 pg/ml (977 - 4542)][87].

The elevated baseline NT-proBNP was not only prognostically relevant but also indicates that these were a congested population, appropriate for enrolment in a study examining changes in congestion over an admission. The median NT-proBNP on day 1 was 3899 pg/ml and reduced to 2486 pg/ml at discharge, a difference that was strongly statistically significant and likely explained by decongestion. This is supported by the observation that on average patients in the current study lost 3.7kg from enrolment to discharge. In the ESCAPE trial patients were decongested to achieve a PCWP ≤15mmHg and a right atrial pressure ≤8mmHg and on average experienced a similar degree of weight loss (-3.6kg)[323]. Patients in several other acute heart failure trials, without haemodynamic knowledge, were observed to have lost less weight at discharge compared with the present study cohort, including in ASCEND-HF (-2.3kg)[28] and EVEREST (-2.1kg)[17], and in real-world data reported from the OPTIMIZE-HF registry of older people admitted with HF (-2.0kg)[324]. LUS B-lines were shown to reduce steadily across four assessments from a maximum point of congestion to a point of clinically judged euvolaemia. On enrolment, the median number of B-lines was high [80 (49 – 124)] both in absolute terms and relative to other studies using the same method to quantify B-lines in patients with acute HF. In studies that have reported total B-lines count, the pre-treatment median number of total B-lines ranges from 23 (7 – 56) to a mean count of 53 ±17[110,325] when LUS was performed at the point of admission. In the current study, there was a sizeable improvement in B-line count when patients received diuretics but the discharge B-line count remained notably elevated [44 (24 – 59)]. The potential for investigator overestimation was mitigated by a core lab process in which no inter-rater difference was observed. Such a finding highlights two important factors about this study cohort. Firstly, they were heavily congested on admission. The study protocol mandated that patients be given at least 12 hours to consider enrolling in the study, during which time the

LUS may have actually reduced from a higher original value at presentation. Patients were also receiving appropriate treatment, as a sonographically apparent improvement in B-lines was observed. Secondly, despite their weights having reduced, there was clear evidence on LUS that congestion persisted in a number of people at discharge. Residual congestion was also apparent on clinical examination, despite an overall improvement in signs and symptoms. While S3 was no longer clinically detectable on auscultation in any patient of 6 patients with a S3 at baseline, the JVP continued to be visible in 31% (5 of 16 people) on discharge. Although evidence of peripheral oedema had resolved in 60% of the cohort, 28% of the participants had evidence of peripheral oedema at discharge. Most tellingly, and consistent with the LUS findings, pulmonary rales continued to be present in 48% of patients, who would have been excluded if respiratory causes such as infection or pulmonary fibrosis had been co-existing with the diagnosis of HF. When signs and symptoms were graded and combined into the composite EVEREST congestion score, the study cohort median value at baseline was markedly elevated [10 (6 – 12)]. Despite a clear reduction with treatment the discharge value remained raised at 3 (1 – 4). In the EVEREST trial sub-analysis that derived the congestion score a median score $\geq$3 identified the cohort at highest risk during follow-up for re-hospitalization for HF or mortality[17].

Interestingly, as the parameters that often guide the assessment of volume status and despite clinically and statistically significant improvements in NT-proBNP and LUS B-lines between enrolment and discharge, neither of these parameters correlated with change in weight across the same intervals. While a close relationship between fluid loss and weight loss would be expected, both these measures of decongestion were modestly correlated in the ESCAPE trial ($r = 0.48$, <0.001), a finding that was also present in sub-analyses of the

DOSE trial and Penn observational study cohorts[326]. Changes in weight in patients during decongestion have been shown to correlate poorly with changes in PCWP ($r = 0.01$, $p = 0.92$)[256]. Only clinical signs and symptoms, amalgamated into the EVEREST composite score were consistently correlated (and modestly so) with change in weight in the current study. The EVEREST composite score combines features of both left and right HF and allows for a broader relation to weight and change in weight which is the end result of chronic fluid accumulation regardless of congestion mechanism (intravascular or tissue predominant or both). While several parameters provided evidence that the study cohort were undergoing decongestion, the apparent lack of relation to each other highlights the absence of a universal standard which accurately and reproducibly reflects volume and pressure status. As outlined before, the complex nature of fluid shifts in congestion is captured as individual components by the different modalities used in congestion assessments, exemplified in hypertensive HF where redistribution of fluid may result in little to no weight loss after aggressive treatment while severe symptoms of dyspnoea and B-lines on LUS may change rapidly.

Given the complex interplay between both intravascular and tissue congestion, no CPM device measure is an exclusive quantification of either phenotype. Conceptually, device S3 is a measure of left ventricular filling pressures and therefore more directed towards an intravascular, pressure-mediated congestion. Thoracic impedance on the other hand reflects the degree to which fluid has accumulated in the lung parenchyma and I propose represents more an assessment of tissue congestion. Tidal volume is also more aligned with tissue congestion, particularly as the CPM device quantifies tidal volume by measuring changes in lung tissue resistance over a respiratory cycle. As people with HF present with tissue,

intravascular or a combination of both phenotypes of congestion it is possible that the sensitivity of the device parameters to detect changes in congestion depends on both the form of congestion as well as the extent of change from baseline. Changes in weight, as described already, are most in keeping with a greater or lesser extent of tissue congestion. Clinical decongestion, without change in weight, suggests redistribution of fluid and most likely intravascular pre-dominant congestion. It follows that in a person who is both intravascularly and tissue congested, the intravascular form may reduce in the first instance, only for plasma refilling to occur with fluid being drawn from the tissue interstitium and decongestion being then apparent more peripherally or within the parenchyma. My interpretation of the correlation analyses is guided by this hypothesis as discussed below.

In the primary analysis, the CPM wearable device demonstrated a correlation between both change in device S3 and change in weight and change in thoracic impedance and change in weight. The magnitude of change in weight was only clinically or statistically notable later in the admission when oral diuretics were commenced and at discharge (visits 3 and 4). The correlation between change in the CPM device S3 and change in weight did not become apparent until discharge. Similarly, the strength of the correlation between change in device thoracic impedance and change in weight was strongest at the switch to oral diuretics and at discharge. The implication is that in this population, the change in volume status within the first 24 hours was not substantial enough to allow the device to effectively detect a difference in congestion but once this had reached a point that would be considered notable (indicated objectively by the extent of change in weight and supported clinically by the physician's decision to de-escalate to oral diuretics or discharge) the correlation became more robust. In the case of device S3, it may have not have been until discharge that on average patients were sufficiently intravascularly decongested to allow for a correlation to

be established. Prior to this point, systemic, tissue decongestion may have been more dominant. That the correlation between thoracic impedance and change in weight became stronger earlier (at visit 3, switch to oral diuretic) than for device S3 (visit 4), indicates that decongestion of the lung parenchyma occurred sequentially before the intravascular decongestion which the CPM device S3 may be more aligned to detect.

In this study, surprisingly, LUS B-lines, and change in B-lines, did not correlate with device thoracic impedance. One possibility is that despite a reduction in B-lines from enrolment to discharge, the observation that patients still had a high level of B-lines evident at discharge meant that the tissue were still congested to such an extent that device measured resistance within the tissues did not change meaningfully enough between assessments to correlate with LUS. On internal analysis of change in the device measures from baseline, thoracic impedance relative to visit 1 only increased significantly at the point of switching to oral diuretics (78.5 ohms versus 70.8 ohms). When change in thoracic impedance and change in LUS B-lines were correlated, the only point at which a relationship potentially appeared was also when diuretics were converted from IV to oral therapy. The implication is that at this point a minimum extent of tissue decongestion was close to being achieved for the device, with the limits of its sensitivity, to be able to detect a difference in pulmonary congestion through a change in the resistance of the parenchyma. That the correlation was neither more powerful or statistically significant is probably explained by an insufficient sample size where more data were required for the device to detect smaller changes in congestion and establish a more robust correlation. LUS B-lines, which correlate highly with extra-vascular lung water[108] is a measure of tissue congestion. There are no published studies correlating LUS B-lines with thoracic bioimpedance as measured by wearable devices. Intrathoracic

impedance as analysed by an indwelling pacing lead sited within the right ventricle has been shown to correlate with B-lines ($r = 0.67$, $p < 0.001$)[327]. In this study of 23 ambulatory patients with HF assessed in the outpatient setting, the mean total LUS B-line count was 6.6 ± 2.2 in patients who subsequently had a decompensation and 0.8 ± 5.5 in patients who remained well, substantially lower than the average count at any assessment in the present study.

CPM device tidal volume was modestly correlated with spirometry tidal volume on day 1 and day of discharge. As described, quantification of tidal volume by the CPM device was based on resistance within the lungs rather than airflow and (as with thoracic impedance) was measured in ohms. One potential explanation for the establishment of a correlation between the two parameters at these time points is that these were the intervals that patients were either at their most or least congested, points at which the device was able to detect and quantify congestion most accurately by measuring at the times of greatest or least parenchymal resistance. I will highlight an important limitation of measuring both parameters in the following section.

The echocardiographic measures can be subdivided into those considered to represent left ventricular filling pressures (E/A ratio, E/e' ratio, mitral valve deceleration time, lLAVI), left ventricular performance (LV GLS, LVOT VTI, LVEF), and intra-cardiopulmonary pressures (PVAT, IVC diameter and TR vmax). While there was a trend towards an improvement in LVOT VTI from being mildly reduced at baseline to within normal range at discharge following treatment, this did not reach statistical significance and LVEF and LV GLS were on average severely impaired throughout the admission without recovery. This is not a surprise finding.

Left ventricular remodelling is a process that occurs over a longer period than a single admission with international guidelines recommending a minimum of 3 months before considering the implantation of a defibrillator in patients with HFrEF to allow the LVEF to improve with treatment[2,328]. The median values of PVAT, TR vmax and IVC diameter were within a range that indicated a low probability for pulmonary hypertension and may not have been subject to meaningful change across the study assessments with decongestion[92]. LAVI was consistently elevated through the study and this level of dilatation is probably also accounted for by the high prevalence of atrial fibrillation and pre-existing HF in the study cohort. Both LAVI and mitral valve deceleration time changed between day 1 and day 2 on IV diuretics suggesting some haemodynamic improvement occurred in left ventricular filling pressures between these two visits but I am cautious with this interpretation as the changes were not sustained in subsequent assessments. Collectively, echocardiographic measures were also poorly correlated with the CPM device measures and where correlations were identified the time points at which there appeared to be a relation between parameters was inconsistent. This is potentially explained by individual variation in the degree to which and when echocardiographic measures change according to loading and volume conditions. A uniform response in these measures to decongestion could not be anticipated, and it is of interest that measures of left ventricular filling pressures (LAVI, mitral valve deceleration time, E/e' ratio and E/A ratio) all showed correlation with S3, the device measure most directed to corresponding intra-cardiac pressures, albeit at different study intervals. It is likely that a larger sample size would have been required to identify change within the echocardiographic parameters across the study visits and for more robust correlations to be established with change in the CPM device parameters.

The effect that sample size and change in sample size had on the correlations between the CPM device and clinical measures is highlighted by the observed relation between thoracic impedance and JVP elevation. On enrolment, when patients were at their most congested, a strong inverse relationship was present between JVP elevation and lower thoracic impedance. At this study point, 22 patients were included in the analysis, a sufficient sample size to establish the correlation. As patients were successfully decongested, the JVP reduced and fewer patients were eligible for this analysis (n = 16 on day 2 of IV diuretics, n = 13 on the day of first oral diuretic, n = 5 at discharge) with consequent loss of power, represented by an incrementally diminished correlation coefficient and greater uncertainty in its value as the p value became steadily larger. This was also the case when examining differences between strength of device S3 in people with or without a S3 on clinical auscultation whereby the reduction of a pool of patients with a clinical S3 restricts interpretation of this analysis to the first two study intervals.

Patients with HF were observed in the REDUCE-HF and CHAMPION trials to live with chronically elevated filling pressures and congestion[50,53]. Minor changes in these persistently raised pressures led to HF decompensation in the COMPASS-HF[42,45]. Relief of symptoms such as acute dyspnoea often precedes and exceeds the resolution of other evidence of congestion, as was reflected in the current study. Approximately 90% of people with NYHA class IV symptoms or constant breathlessness on the EVEREST scale at baseline had resolution of these symptoms by discharge compared with up to 48% of people continuing to have a physical sign of congestion and a markedly elevated LUS B-line count. The discordance between degree of reduction in symptom burden and objective evidence of congestion may account for the overall poor correlation between symptoms and device

measures. For instance, the only clinical parameter that demonstrated a relationship with thoracic impedance was change in total EVEREST score, a composite of symptoms and signs that relate to predominantly tissue congestion, which was only apparent when people were at their most systemically decongested. This finding of a relationship between thoracic impedance and a clinical parameter becoming evident at the point of greatest decongestion is consistent with the analyses of change in thoracic impedance and change in weight, and between thoracic impedance and NT-proBNP and to a lesser extent LUS B-lines.

The CPM wearable device demonstrated strong correlation with clinical heart rate and ECG parameters, including heart rate and QRS duration. In the SHIFT trial a clear association between higher resting heart rate (≥87bpm) and a two-fold increase in cardiovascular death or HF hospitalization was observed in patients with HFrEF who were in sinus rhythm[329]. The importance of this prognostic association is recognised in the contemporary ESC guidelines for HF which recommend targeting a sinus rhythm heart rate below 70bpm with beta-blockers or ivabradine[2]. Higher resting heart rates, particularly in atrial fibrillation, are also a common contributor to suboptimal response to cardiac resynchronization therapy and the ability to determine heart rate accurately using the CPM device would provide healthcare providers with additional opportunity for implanted device optimization especially when remote downloads from implanted devices are often limited to every 6 months in most UK centres[330,331]. In a combined analysis of the PARADIGM-HF and ATMOSPHERE trials, QRS duration at baseline was associated worse clinical outcomes, with incident broadening of the QRS to ≥130ms across follow-up being associated with a 49% increase in subsequent cardiovascular mortality or hospitalization for HF[332]. Broadening of the QRS may also indicate the development of left bundle branch block that will develop in approximately

2.5% of patients with HFrEF per year and provides an indication for cardiac resynchronization therapy[331,332]. The Rhythm algorithm assessed the ECG for the presence of p waves and stability of the R-R interval, determining if both were absent that the ECG was positive for potential atrial fibrillation. The ability of the device to determine if a heart rhythm was irregular was strongly in agreement with clinical pulse irregularity. Atrial fibrillation is common in people with HF and is associated with worsening HF and increased rate of mortality. Early detection of atrial fibrillation may allow for anti-coagulation to be initiated promptly, limit the potential for uncontrolled tachy-arrhythmia related decompensation and inform early decision-making regarding rhythm or rate control strategies. While the CPM device Rhythm parameter was effective at detecting potential arrhythmia, the comparator with clinical pulse regularity had potential for an underestimation in the level of agreement. The presence of ectopic beats, which are not uncommon in patients with HF, may have been a confounder if the Rhythm parameter (appropriately) designated a negative result to a rhythm with premature ventricular contractions that made the pulse feel irregular clinically. I did not have access to the CPM device ECG strips to confirm whether this occurred.

7.5 Limitations

As with any proof-of-concept study, there was potential for the sample size to affect the strength of the correlations observed and to have a bearing on the statistical significance of the results. The analysis of reducing numbers of patients with an elevated JVP across studies leading to a smaller correlation coefficient and larger p value when analysed with thoracic impedance provides such an example. The original power calculation determined that 40 patients should be recruited in this cohort. This sample size estimation accounted for the

potential for patients to be withdrawn allowing for the high risk, frail population that was anticipated to be recruited. In total, four final visits did not occur meaning an analysis with the estimated point of greatest decongestion (day of discharge) was not possible in these patients. In several analyses, the correlation between thoracic impedance and clinical parameters appeared to be strongest when patients were at their most decongested. With 16% of the sample not undergoing the final study assessment, there may have been insufficient power to determine stronger, more statistically significant relations with a broader range of clinical parameters. For the same reasons, the sample size may have affected the analyses of change in variables. The research ethics committee requested that patients be given at least 12 hours to consider participation. During this time period, which effectively meant a change in calendar day between approach and enrolment, patients would have decongested further so the first assessment was conducted when patients had had a partial response to treatment. However, the counterpoint to this is that patients had their final assessment on the day of discharge and so the point of clinically determined euvolaemia was definitively captured. However as outlined above in the Discussion, despite the time between approach and the first assessment, this was still a heavily congested population at baseline with evidence of volume removal across the study that was consistent or greater than previous reports in patients receiving treatment for decompensated HF. Arguably, it was more important to capture change at the final interval, day of discharge, as this is the volume state relevant to how patients would be applying the device when at home. It was not possible to perform spirometry and a device reading at the same time because motion artefact could cause interference with the device signals. It is possible that in people with pulmonary congestion, there is variability in the depth and rate of breathing and tidal volumes in both comparator assessments may consequently have

been different, reducing the strength of the correlation. I will discuss the impact of the COVID pandemic on the study as a whole in the General Discussion chapter.

7.6 Conclusions

In this study of congested patients admitted with HF, the CPM wearable device thoracic impedance and S3 correlated with change in weight, and with clinical heart rate and rhythm. Overall, the correlation between the device and clinical parameters appeared to be strongest when patients were at the point of clinically determined euvolaemia on the day of discharge.

8. CHAPTER EIGHT. General discussion

8.1 Impact of the COVID pandemic and regulatory approvals.

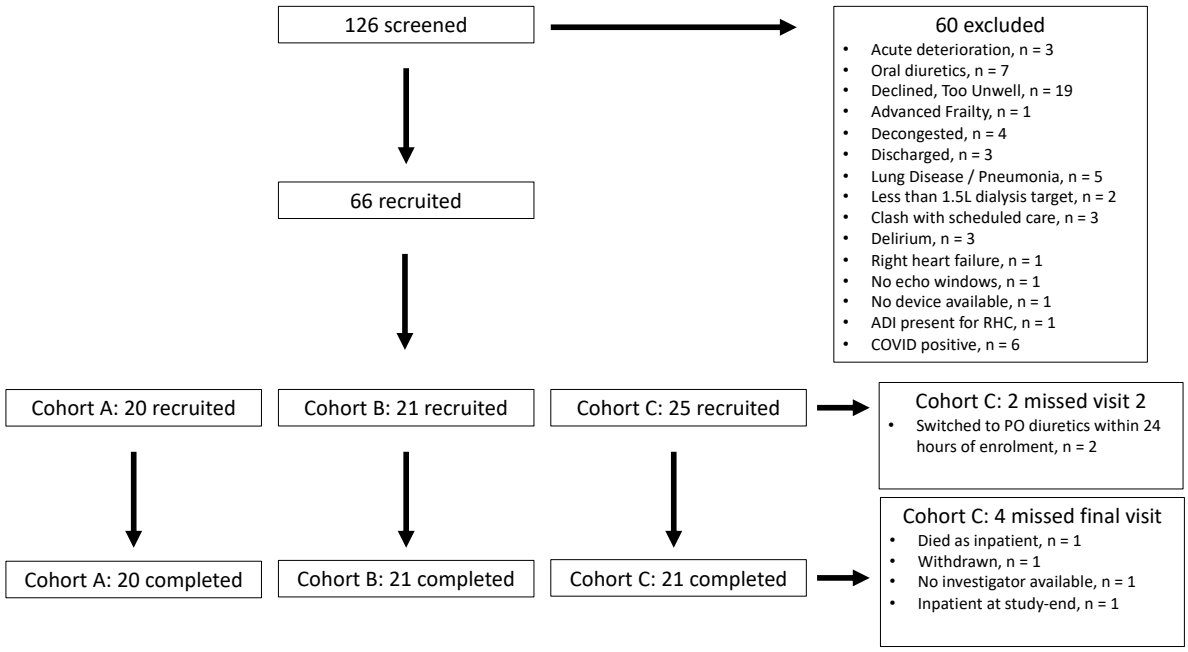
I moved to Glasgow and started this PhD project in February 2020. By March 2020 the WHO had declared the COVID outbreak as a pandemic and the UK went into its first lockdown. As a result, while I was able to draft the study protocol, research ethics application and supplementary documents such as the study SOPs and patient information leaflets, all essential stages required for commencement of the project were delayed. During the pandemic, ADI ceased much of its development on the final algorithms used in the wearable sensor. Notably, this led to delays compiling and submitting an application to the MHRA for regulatory approval of this non-CE marked device. The MHRA application was a joint enterprise between the UOG researchers and ADI. It was the first time the UOG group had co-authored such an application for a device study and included several thousand pages of documentation, outlining the study design, preparatory work, and extensive device development and technical detail. The project received approval from the MHRA on 30th July 2021, final ethical from the London-Dulwich research ethics committee on 3rd August 2021 and the NHS GG&C Sponsor's approval with "green-for-go" on 23rd September 2021 allowing recruitment of the pre-study training cohort to begin. On the 28th September 2021 a minor device deficiency occurred in a Training Cohort patient relating to inputting of a time-stamp onto a device using the Base Station Simulator software. A notification to the MHRA and subsequent pause in study activity meant recruitment started again on 17th November 2021. After completion of the training cohort, the first patient was subsequently recruited into CONGEST-HF on 26th November 2021.

All patients recruited into CONGEST-HF were by definition high-risk cohorts during the pandemic because they had either serious cardio-respiratory disease (HF) or end-stage renal failure. In particular, Cohort A were assessed on a transplant ward where immunocompromised patients were being looked after. 6 of 126 (4.8%) patients screened were excluded due to subsequently testing positive for COVID. I contracted COVID on two occasions (January 2021 and May 2021) during the active recruitment period of the study, resulting in two 2-week pauses in study clinical activity.

8.2 Study recruitment

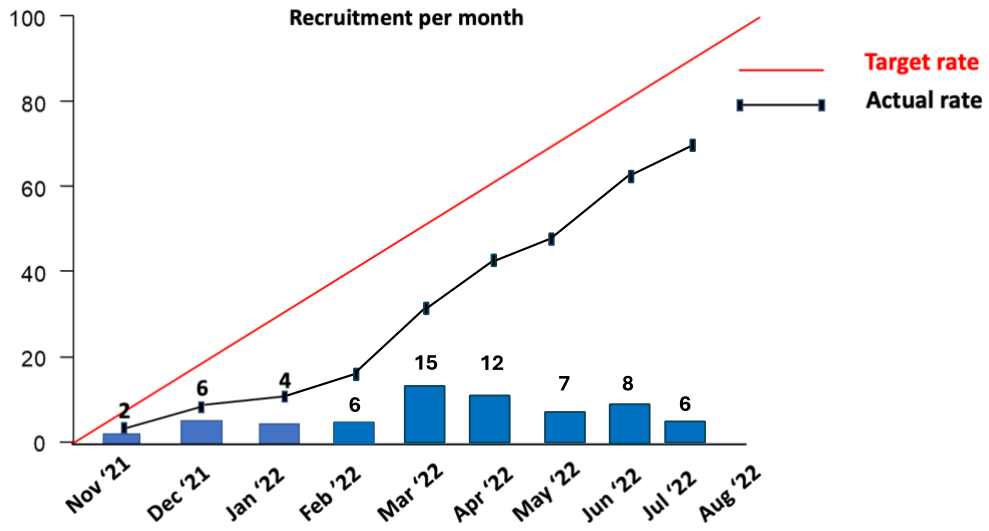
126 potentially eligible patients were screened, of whom 66 (52.4%) were recruited, and represents an acceptable approach to enrolment ratio when compared with studies in general, particularly during a pandemic. Screening and recruitment numbers for CONGEST-HF are detailed in **Figure 8-1**.

Figure 8-1 CONSORT diagram of screening and recruitment in the CONGEST-HF study



As outlined, factoring in delays to study commencement and several necessitated pauses in recruitment, I was not able to recruit the full target of patients into Cohorts B (21 of 40 recruited) and C (25 of 40 recruited) during the remaining period that the study was funded for. The monthly rate at which patients were recruited compared with target recruitment is outlined in **Figure 8-2**. 156 study visits contributed data to this thesis, performed at an approximate rate of 1 study visit per 1.5 days during the active recruitment period from the end of November 2021 to July 2022.

Figure 8-2 Actual and target recruitment rates during the CONGEST-HF study



8.3 Summary of findings

In Chapter 2, I reported the methods and findings of an original meta-analysis that I conducted using data extracted from the key randomised controlled trials that examined the effectiveness of implantable haemodynamic monitors to guide treatment in patients with HF. I found that among people with left ventricular systolic dysfunction, treatment guided by implantable monitors reduced HF-related events but the same benefit was uncertain in people with HFpEF, due in part to smaller numbers of these patients being enrolled in the trials.

In the CONGEST-HF study, I examined the effectiveness of the CPM wearable device at detecting congestion in three different cohorts who were at risk of or actively receiving treatment for volume overload. I performed a multi-modal congestion assessment at each of the 156 study visits, including LUS, echocardiography, bedside spirometry, biomarkers, physical signs and symptoms examination and the wearable device readings.

As outlined in Chapter 5, I recruited 20 patients who were undergoing a clinically-indicated RHC into Cohort A. A broad range of haemodynamic states were observed, with the obtained median values within the generally accepted normal range for intra-cardiopulmonary pressures. Measured at a single time-point, the range of CPM device S3 values showed less variation than the PCWP values and CPM device S3 did not correlate PCWP. CPM device thoracic impedance and tidal volume did not correlate with haemodynamic pressures either. As I discussed in Chapter 4, a discordance has been observed between haemodynamic pressure and volume in several studies correlating estimated pulmonary pressures from implanted sensors with total body volume[219,285,333]. In

this current study cohort there was an observed correlation between LUS B-lines (a marker of both intravascular and extravascular congestion) and each of the CPM device parameters – S3, thoracic impedance and tidal volume. In this advanced HF cohort, with echocardiographic evidence of diastolic dysfunction, a clinical S3 was detected in 40% of people despite apparently normal range haemodynamics. Device S3 was higher in patients with a clinical S3 compared to those without S3 on auscultation.

As reported in Chapter 6, in Cohort B, I recruited 21 patients with end-stage renal disease who were undergoing at least 1.5L volume removal by haemodialysis. A clinically important amount of volume (2L) was removed on average. Patients were assessed pre-dialysis and post-dialysis. In this cohort, CPM device thoracic impedance was strongly correlated with LUS B-lines both before and after volume was removed. Change in thoracic impedance was modestly correlated with the volume of fluid removed by dialysis, the same relationship was of borderline significance when CPM S3 was correlated with the amount of volume removed.

In Chapter 7, I reported the study examining the CPM device in 25 patients admitted to hospital for decompensated HF who were receiving IV diuretics. I performed study assessments at four intervals, from the point of greatest congestion (day 1) to the point of greatest decongestion (day of discharge). Across these time points, CPM device thoracic impedance and S3 were correlated with change in weight but this relationship was only apparent when people were at the point of greatest decongestion as determined by their treating physicians (day of discharge).

Overall, across the three cohorts, CPM device tidal volume demonstrated modest correlation with tidal volume obtained from a bedside spirometer. As described in the Limitations sections of each Results chapter, I cannot completely discount that the strength of the correlation would have been different if the two tidal volume assessments were performed at the exact same time but this was not feasible due to the potential for motion artefact to interfere with the device readings.

Echocardiography parameters did not change substantially across serial measures and indicate that this may not be a robust modality to accurately trend changes in volume. There appeared to be relationships between echocardiographic parameters of left ventricular performance or estimated filling pressure and device S3 (eg LVOT VTI, LV GLS, mitral valve inflow deceleration, E/A ratio, E/e') and between measures of pulmonary pressures (TR vmax, PVAT) and device thoracic impedance. However, these correlations were not consistent across cohorts or study intervals.

Across cohorts, the CPM device heart rate detection was correlated with either clinical or ECG measured heart rate. The device Rhythm algorithm was also accurate at ruling out potential atrial fibrillation and effective at detecting the potential for atrial arrhythmia to be present.

8.4 Device safety and performance

The anticipated risk to patients from this study was low. Accordingly, there were no device-related adverse events during or following any application of the CPM wearable device. Of greatest importance in this population in whom implanted cardiac devices are common, and

a strength of the study monitoring for adverse events, was that I examined in real-time pacemaker or defibrillator EGMs while the CPM wearable device readings were being performed. No device-device interaction was observed.

6 device deficiencies were recorded, none of which posed a risk to patient safety. 2 deficiencies were related to adhesives peeling and indicate that depending on body shape the device may not align satisfactorily on all people factoring in environmental conditions (eg humidity) as well. 3 device deficiencies were related to loss of a device signal, 2 of which were in the same device which was deemed faulty and excluded from the study. 1 device deficiency was due to poor connection between the mobile App and the device and may have been due to transient dropout of signal and was easily rectified by resetting the device.

8.5 Future directions

The CONGEST-HF study was an exploratory, observational study assessing the effectiveness of the wearable device to detect congestion. Most of the patients enrolled were actively congested and undergoing decongestion. In this sense, particularly in Cohort C (the intended population for the device use), the CONGEST-HF study was an examination of the device in a "wet-to-dry" direction of clinical status. While there is clinical utility in understanding how sensitive the device is to changes in congestion, remote monitoring devices are intended to detect alterations that indicate rising risk of decompensation, or a "dry-to-wet" direction. The Correlation of Non-invasive CPM Wearable Device With Measures of Congestion in Heart Failure in Exercise (CONGEST-HF-Ex) study (ClinicalTrials.gov ID NCT06393842) is currently enrolling patients. CONGEST-HF-Ex will evaluate both the accuracy of the device to

detect an anticipated rise in filling pressures following exertion in people with HF and will separately serially assess patients undergoing dialysis to include a “decongested-to-congested” assessment. I co-authored the CONGEST-HF-Ex protocol. In a separate study being conducted in India, the device is being examined in people with chronic HF who are at home until the point of hospitalization to determine how the device parameters change during decompensation. These studies along with the contribution of the current CONGEST-HF study, provide a large quantity of data for the manufacturer. Potential uses of this repository of clinically obtained data include using neural network machine learning to refine the device analytic algorithms and optimize its performance, possibly to derive and validate a weighted congestion score and threshold for device alerts to be developed similar to other multi-parametric devices[79,87]. Ultimately, to support its use in routine clinical practice and achieve inclusion in HF guidelines, the CPM device needs to be examined in a randomized controlled trial, investigating whether treatment guided by the device is superior to standard treatment alone at reducing clinical endpoints such as HF hospitalization. The highest achievement for the device would be to empower patients to engage more proactively in their self-management and titrate medications such as diuretics in a personalized regimen, such as is the case for diabetics who adjust insulin doses to glucose reading machines. The effectiveness of the device will not only be determined by how accurately it can detect congestion but also how much patients comply with using it, a broader limitation of wearable devices influenced by the device design, applicability, required frequency and duration of use, connectivity and patient factors such as cognitive level, dexterity and technology literacy.

8.6 Conclusions

The CPM wearable device did not correlate with invasive haemodynamics. However, modest to strong correlation was observed between CPM device thoracic impedance and measures of total body volume (intravascular and extravascular congestion), including LUS B-lines, volume of fluid removed by dialysis and change in weight. The CPM device S3 was a marker for left ventricular performance or diastolic dysfunction on echocardiography but the strength of this correlation was modified by the cohort examined. In patients with decompensated HF, both device thoracic impedance and S3 appeared to correlate with clinical measures of congestion when patients were at the point of greatest decongestion.

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APPENDIX

University of Glasgow
Institute of Cardiovascular & Medical Sciences

Golden Jubilee National Hospital
Patients at the heart of progress

NHS Greater Glasgow and Clyde

CONSENT FORM

Study title: Correlation of the non-invasive Cardiopulmonary Management (CPM) wearable device with measures of congestion in heart failure- CONGEST- HF

Summary title: The CPM wearable device and measures of congestion study.

To be completed by the **PARTICIPANT. Please use INITIALS to mark YES or NO**.

Participant number: _____ **Date:_____**

Declarations	YES	NO
I have read and understood the information leaflet, Version 2.2 01/12/21		
I have had the opportunity to discuss the study, ask questions about the study and I have received satisfactory answers to all my questions.		
I understand that I am free to withdraw from the study at any time without giving a reason and this will not affect my future medical care.		
I agree to allow the researchers use my information as part of this study as outlined in the information leaflet. I agree to allow the researchers, NHS sponsor trial monitors and, if required, government regulatory groups access to my medical records as part of this study.		
I consent to have my data processed, including the sharing of data with third parties such as Analog Devices Inc, as part of this research study as outlined in the information leaflet.		
I consent to have my data transferred outside the European Economic Area (EEA), as part of this research study as outlined in the information leaflet.		
I consent to my data being used for regulatory or commercial purposes as outlined in this leaflet .		
I consent to have my data held by the University of Glasgow's Robertson Centre of Biostatistics for the purpose of this study.		
I agree for my GP to be informed about my participation in this study		

I agree to give a blood sample(s) as part of this study and for future analyses.		
I agree to have an echocardiogram, lung function test and lung ultrasound as part of this study.		
I agree to allow my data to be used in anonymised format for presentations or publications		
I consent to take part in this research study having been fully informed of the risks, benefits and purpose of the study		

Participant's Name (Block Capitals):	
Participant's Signature:	
Date:	

To be completed by the **RESEARCHER**. **Please use INITIALS to mark YES or NO**.

Participant number: _____

Declarations	**YES**	**NO**
I have fully explained the purpose and nature (including benefits and risks) of this study to the participant in a way that he/she could understand. I have invited him/her to ask questions on any aspect of the study.		
I confirm that I have given a copy of the information leaflet and consent form to the participant.		

Researcher's Name (Block Capitals):	
Researcher's Title & Qualifications:	
Researcher's Signature:	
Date:	

1 copy to the patient, 1 copy to the researcher for site file, 1 original for the patient's notes

University of Glasgow
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NHS Greater Glasgow and Clyde

PARTICIPANT INFORMATION LEAFLET

Study title: Correlation of the non-invasive Cardiopulmonary Management (CPM) wearable device with measures of congestion in heart failure- CONGEST- HF

Summary title: The CPM wearable device and measures of congestion study.

Chief Investigator and Co-investigators:
Chief Investigator: Dr Pardeep Jhund, University of Glasgow
Co-investigator: Professor Mark Petrie, University of Glasgow
Co-investigator: Professor Roy Gardner, University of Glasgow
Clinical Research Fellow: Dr James Curtain, University of Glasgow

You are being invited to take part in a research study being conducted at the Queen Elizabeth Hospital, Glasgow. Before you decide whether or not you wish to take part, you should read the information provided in this leaflet carefully. Take time to ask questions – don't feel rushed or under pressure to make a quick decision. You should understand the risks and benefits of taking part in this study so that you can make a decision that is right for you. You may wish to discuss it with your family, friends or GP.

PART 1 – THE STUDY

Why is this study being done?

This study is being done to assess how effective a newly developed wearable medical device, called the CPM wearable device, is at measuring how much congestion (excess fluid) a patient has in their body.

The build-up of congestion is a major feature of heart failure and can lead to hospitalisation. Patients with congestion often require a prolonged inpatient admission for intravenous diuretics and decongestion.

Recognising changes in excess fluid status either before a patient becomes unwell or during decongestion treatment is highly desirable so that timely treatment can be started or so that treatment can be adjusted based on an individual's response to therapy.

The ability to assess patients by applying a single, non-invasive wearable device would potentially provide a useful tool for assessing a patient's congestion levels. Analog Devices Inc, the device manufacturer and the study's commercial funder, have developed a wearable patch-like device called the CPM wearable device to assess congestion levels. This study will compare the measurements the wearable device provides with the results from other standard ways of measuring congestion.

Why am I being asked to take part?

You are being invited to take part in the study because you have been admitted to hospital with a diagnosis of heart failure. While you are on intravenous diuretics we expect you to have changes in levels of congestion that can be assessed in this study. This will be done by using standardised tests of fluid volume status that will be compared with the findings of the CPM wearable device.

Do I have to take part? What happens if I say no? Can I withdraw?

No, you don't have to take part in this study. If you decide not to take part it won't affect your current or future medical care. You can change your mind about taking part in the study and opt out at any time even if the study has started. If you decide to opt out, it won't affect your current or future medical care. You don't have to give a reason for not taking part or for opting out. If you wish to opt out please contact Dr James Curtain, by email or phone, on the details outlined in the Contacts section below.

If during your hospital admission you become unable to provide consent to continuing in the study (for instance if you developed a confusion called "delirium") then you will not be assessed as part of the study again until such time that you are able to consent again.

Your data collected as part of the study up until the point that you are withdrawn will still be used unless you state that you want your data withdrawn as well.

How will the study be carried out?

The study assessments will take place on the day of your enrolment in the study (day 0), 24 hours later on day 1, on the day you are changed from intravenous to oral diuretics and on the day of your discharge from hospital. Standard tests of congestion such as echocardiography, lung function breathing tests and lung ultrasound will be performed on each of these days. Additionally, we will be taking blood samples at the same time as blood tests are being ordinarily taken as part of your inpatient care. We will take an additional 1-2 teaspoons of blood. We will ask you to wear the CPM wearable device at each time you are assessed during the study and will take recordings of the measurements it provides. We will compare the findings of the device with the other measurements of congestion taken during your evaluation. We aim to recruit 40 patients admitted to the Queen Elizabeth University Hospital with heart failure.

What will happen to me if I agree to take part?

Participation in the study will not influence or change the medical care you receive.

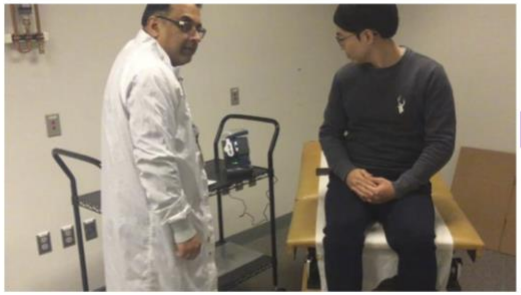
Should you agree to take part in the study, the study research fellow will take details on your symptoms and will carry out a standard physical examination. They will also take some information from your patient records regarding your relevant medical history.

As mentioned above, standard tests of congestion will be performed. The table below outlines specifically (a) what tests will be performed as part of the study, (b) whether these tests are part of your standard care or related to the study only, (c) how long each test usually takes, (d) who will perform the test.

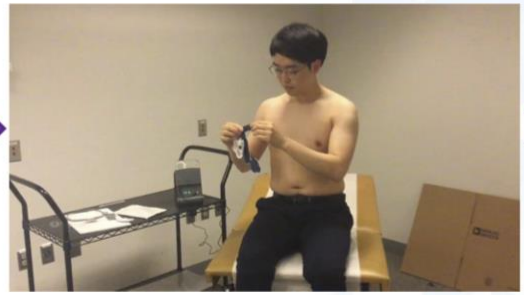
Study Investigation / Procedure	**Is this part of your standard medical care?**	**How long does it take?**	**Who will perform it?**
Echocardiogram	Yes, if medically required. Otherwise, no	30 minutes	The Clinical Research Fellow
Lung Ultrasound	No	10 minutes	The Clinical Research Fellow
Lung function (breathing) test	No	10 minutes	The Clinical Research Fellow
Blood samples	Yes	5 minutes	Phlebotomist or the Clinical Research Fellow
Physical Examination	No	10 minutes	The Clinical Research Fellow
CPM wearable device reading	No	15 minutes	The Clinical Research Fellow

The images below demonstrate the process of making a CPM wearable device reading.

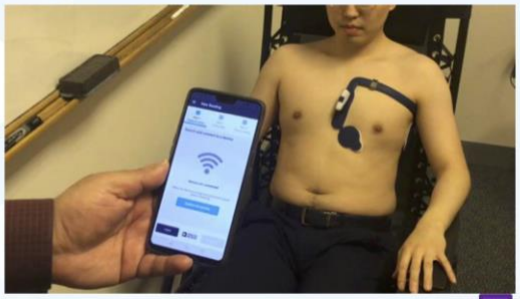
Clinical Prototype Demonstration



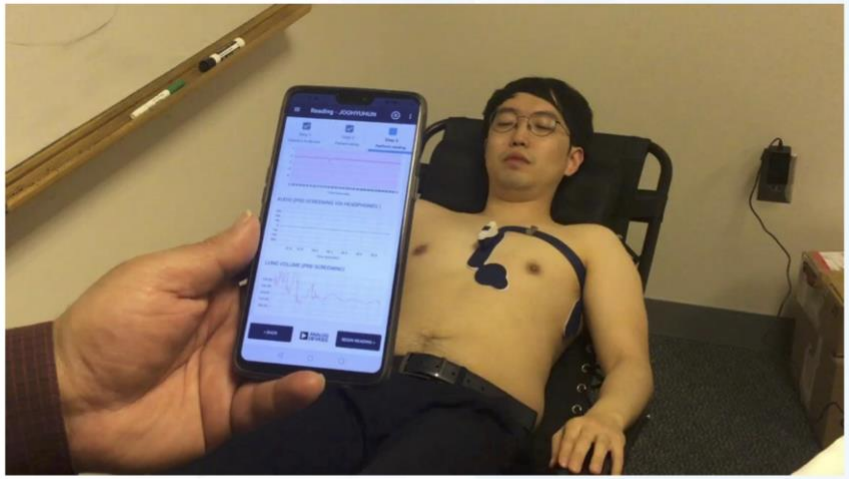
Prep Adhesive



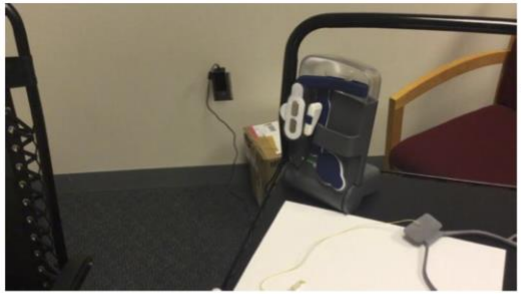
Place Wearable



Connect App



Measurement



Upload Measurement

Are there any benefits to me or others if I take part in the study?

No. Participation in the study will not influence or change the care you ordinarily receive. If the research produces incidental findings (previously undiagnosed conditions that are discovered unintentionally) of clinical significance, you will be informed of the results and offered appropriate follow-up and treatment as per current best standard practice.

If the CPM wearable device is shown to be a safe and reliable tool for assessing congestion levels further studies will be performed using it which may lead to its wider use among heart failure patients.

Are there any risks to me or others if I take part in the study?

As participation in the study will not influence or change the medical care you receive we do not foresee any significant risk to enrolled participants. There is a small risk of an allergic reaction to the wearable device when applied to the skin. There will be an independent safety monitoring process to record and analyse the risks of any issues with the device if they arise. Within 48 hours after your assessment a researcher will check on you (and within 48 hours by phone call if you have gone home) to ensure you have not experienced a delayed reaction to the device adhesive. If you have a pre-existing implanted device such as a pacemaker, that device will be checked at the time of the CPM wearable device reading to ensure no adverse interaction between the two devices takes place. Similarly to when performing a heart ECG tracing, male participants may require some chest hair to be shaved by the researchers beforehand to ensure the wearable device contacts well with the skin.

Blood sampling is already performed during your medical care. We will take an additional 1-2 teaspoons of blood as part of the assessment.

Will I be told the outcome of the study? Will I be told the results of any tests or investigations performed as part of this study that relate to me?

Following the completion of the study, the research team will provide a lay summary of the results on request. The research team can be reached using the contact details provided at the end of this information sheet. The study results will also be available on the Institute of Cardiovascular and Medical Sciences website- https://www.gla.ac.uk/researchinstitutes/icams/research/bhfcoeglasgow/corefacilitiesandinnovativeplatforms/. All published results will use non-identifiable data.

As part of the study assessment you will have the opportunity to ask about the results of the tests taken during your evaluation. To ensure the reliability of the study, the investigators and patients will not have the findings from the CPM wearable device revealed to them at the time of taking the measurements.

PART 2 – DATA PROTECTION

What information about me (personal data) will be used as part of this study? Will my medical records be accessed?

Your medical records will be accessed to determine if you are suitable to participate in the study. Baseline information including age, gender, race, height and weight will be collected. Previous or current relevant

medical problems will be recorded along with your current list of medications. The results of tests you have will be recorded and used to compare with the CPM wearable device measurement.

If you agree to take part in the study only NHS sponsor study monitors, government regulatory authorities and the research doctors will have access to your medical records.

Will my personal data be kept confidential?

Yes. The data collected is the minimum amount of data required to conduct the study. We will not use the data collected for anything other than the research that has been described in this leaflet. Any information about you that leaves the hospital will have your name and address removed so that you cannot be recognised from it. A research ethics committee have approved the study, including the proposed handling of data. Researchers from the University of Glasgow collect, store and process all personal information in accordance with the General Data Protection Regulation (2018). The University of Glasgow's Robertson Centre for Biostatistics will manage your data during this study.

We will be using information from you and/or your medical records in order to undertake this study. This means that we are responsible for looking after your information and using it properly. Your non-identifiable study data will be stored electronically on the Glasgow Clinical Trials Unit's secure server held at the Robertson Centre for Biostatistics. The University of Glasgow will keep identifiable information about you for 10 years after the study has finished.

Paper copies, such as your consent form, will be kept securely in a locked cupboard in a designated research office and then archived on behalf of the NHS Sponsor. The consent form will be scanned and held securely in electronic format on the NHS Greater Glasgow and Clyde network. The consent form will also be held on behalf of the NHS Sponsor on the Glasgow Clinical Trials Unit's secure server. All paper documents will be securely archived on behalf of the NHS sponsor on completion of the project. Electronic records will be kept on a password protected computer. Study data will be held in non-identifiable form using unique study IDs.

Study data may be made public and used as part of a professional presentation at a medical conference or as part of a publication in a peer-reviewed medical journal. Data that is made public will not contain any of your personal or identifiable details. Based on the findings of the study, Dr James Curtain, the study Clinical Research Fellow, will submit a thesis for the award of the post-graduate research degree Doctor of Medicine (MD) from the University of Glasgow.

Since it is important that we make the most of medical research data, we may in future share data from the study with other researchers, both in the UK and in other countries, including outside the European Economic Area (EEA). No personal data will be shared.

Analog Devices Inc, the company who make the wearable device, are based in both the UK and USA. We will share the non-identifiable device data with Analog Devices Inc so that the information collected can be processed. In doing so, non-identifiable and encrypted data may be transferred outside the EEA. Analog Devices Inc will not have access to your medical records or identifiable information. At the end of the study, the NHS sponsor will release the complete study results to be shared with Analog Devices Inc using non-identifiable data. Non-identifiable data may also be used for regulatory or commercial purposes.

Your rights to access, change or move your information are limited, as we need to manage your information in specific ways in order for the research to be reliable and accurate. If you withdraw from the study, we will

keep the information about you that we have already obtained. To safeguard your rights, we will use the minimum personally-identifiable information possible.

You can find out more about how we use your information by contacting the research team using the details outlined in the Contacts section below.

Will my GP be informed if I take part in the study?

It is standard practice to inform GPs if their patient is taking part in a study. We will write to your GP and inform them about your participation. They will not be involved in conducting the study but will be given the same contact details to access researchers. We will not be informing GPs about the results of any assessments or the overall end results of the study.

PART 3 – COSTS, FUNDING & APPROVAL

Will I be paid anything if I agree to take part?

No. Participation in this study is voluntary and no payments will be made to participants. Transport costs may be reimbursed for study participants where transport is required specifically for study assessments.

Who is funding this study? Will the results be used for commercial purposes?

This research is being sponsored NHS Greater Glasgow & Clyde. The study is funded by Analog Devices Inc who have developed the CPM wearable device. The results of this study may lead to further research using the CPM wearable device in larger groups of patients. Non-identifiable data may be used for commercial or regulatory purposes.

Has this study been approved by a research ethics committee?

The study has been approved by a research ethics committee, who support that it meets ethical guidelines for medical research. Ongoing ethical good practice is a condition agreed with the research ethics committee.

PART 4 – FURTHER INFORMATION

What happens if something goes wrong during the study?

The researchers take the safety and well-being of participants very seriously. While we expect this study to be low in risk to participants, any adverse events related to the device will be recorded. The researchers and NHS sponsor will examine these events and whether it is safe to proceed with your involvement and the study in general. Device related adverse events are reported by the researchers to the Medicines and Healthcare Products Regulatory Agency (MHRA).

This study is sponsored by NHS Greater Glasgow & Clyde. The NHS Sponsor has insurance cover for negligent harm provided under the Clinical Negligence and Other Risks Indemnity Scheme (CNORIS). The University of Glasgow provides insurance cover for harm relating to the design of the study. The device manufacturer, Analog Devices Inc, provides indemnity for harm caused by the CPM wearable device.

If you believe that you have been harmed in any way by taking part in this study, you have the right to pursue a complaint and seek any resulting compensation through the NHS Greater Glasgow and Clyde who are acting as the research sponsor. Details for the NHS Greater Glasgow and Clyde complaints department are detailed in the contacts section at the end of this information sheet

What happens if I wish to make a complaint?

Should you have a complaint or wish to withdraw from the study at any stage, in the first instance please contact the study's Chief Investigator, Dr Pardeep Jhund, on the contact details provided in the contacts section of this information sheet. If you have concerns about any aspect of this study, you can speak to the researchers (office hours are Monday-Friday 9am-5pm).

Also, as a patient of the NHS, you have the right to pursue a complaint through the usual NHS process. To do so, you can submit a written complaint to the Patient Liaison Manager, Complaints Office using the details provided in the contacts section below. Note that the NHS has no legal liability for non-negligent harm. However, if you are harmed and this is due to someone's negligence, you may have grounds for a legal action against NHS Greater Glasgow and Clyde but you may have to pay your legal costs.

Where can I get further information?

Further information regarding any aspect of the study is available from the study's Clinical Research Fellow, Dr James Curtain on the contact details in the following section.

If you would like further information about research in general, Dr Matthew Lee, Clinical Lecturer at the University of Glasgow, can answer your questions. His contact details are provided in the contacts section below.

You are encouraged to ask questions at any time during the study.

Study Research Team and Contact Details

Dr James Curtain, Clinical Research Fellow
Address: BHF Glasgow Cardiovascular Research Centre, 126 University Place, Glasgow, G12 8TA
Tel: xxx-xxxxxxxx (study mobile) Email: James.Curtain@glasgow.ac.uk

Dr Pardeep Jhund, Consultant Cardiologist
Address: BHF Glasgow Cardiovascular Research Centre, 126 University Place, Glasgow, G12 8TA
Tel: xxxx xxxxxxx Email: Pardeep.Jhund@glasgow.ac.uk

Professor Mark Petrie, Consultant Cardiologist
Address: BHF Glasgow Cardiovascular Research Centre, 126 University Place, Glasgow, G12 8TA
Tel: xxxx xxx xxxx Email: Mark.Petrie@glasgow.ac.uk

We have an advisor from the university who you can contact for information on research in general.

Dr Matthew Lee, Clinical Lecturer
Address: BHF Glasgow Cardiovascular Research Centre, 126 University Place, Glasgow, G12 8TA
Tel: xxx-xxxxxxxx (work mobile) Email: Matthew.Lee2@glasgow.ac.uk

Thank you for taking the time to read this leaflet and for considering taking part in the study.

Lung Ultrasound Standard Operating Procedures – CONGEST-HF

Rationale: Lung congestion

Estimated duration: 5-10 minutes

Patient position: Semi-recumbent (~45-degree angle – as able)

Presence/absence of the following noted (can affect lung ultrasound findings):

- LVAD, current chest drain(s), current pneumothorax, current pulmonary contusion(s), current pneumonia/ARDS, current lung cancer, known pulmonary fibrosis, advanced COPD, advanced hepatic failure

Probe: Transducer phased array

Frequency: A range of frequencies (estimated range 2.25 to 4.25MHz)

Pleural effusion: Presence/absence will be documented for right and left lungs.

Zones: Eight zones (four zones on each hemi-thorax)

	Anterior (between sternum and anterior axillary line)		Lateral (between anterior and posterior axillary line)	
Right lung	Zone 1 (upper)	Zone 2 (lower)	Zone 3 (upper)	Zone 4 (lower)
Left lung	Zone 5 (upper)	Zone 6 (lower)	Zone 7 (upper)	Zone 8 (lower)

Gain adjustment: Allows for optimal visualisation of pleural line and B-line artefacts

Imaging depth: 18 cm (may require adjustment depending on habitus)

Image storage: Electronically on password protected securely encrypted hard drive

Video clips: Recorded for 6 seconds

De-identification: Unique study identifiers only

Analysis: We will count the maximum number of B-lines in a single intercostal space for each zone

Echocardiography Standard Operating Procedure – CONGEST-HF

Rationale: Cardiac structure and function, estimation of cardiac filling patterns
Patient

- **Position:** Left lateral decubitus (parasternal & apical), supine (subcostal)
- **Height, Weight, Body Surface Area (DuBois formula):** Recorded

Ultrasound

- **Probe:** Transducer phased array
- **Gain adjustment and Imaging depth:** Allows for optimal visualisation
- **Video clips:** Recorded for ≥3 full cardiac cycles, 6 cardiac cycles if in atrial fibrillation or frequent PVCs
- **Storage:** Electronically on machine ± server, and securely held locally approved memory stick / hard drive

#	Window	Technique	Findings/Values	Notes
1	PLAX	Cine (plain)	LA Diam	
2		Colour on AV	AR?	
3		Colour on MV	MR?	
4		M-Mode LV	IVSd, LVIDd, LVPWd, LVIDs, LVEF, (LVEDV, LVESV)	
5		M-Mode Ao/LA		
6		Aortic root & ascending aorta	LVOT Diam	
7		RV inflow		
8		Colour on TV	TR?	
9		Doppler CW TV	TR Velocity	
10	PSAX	AV/TV/PV: Cine (plain)		
11		Colour on AV	No. of leaflets, AR?	
12		Colour on TV	TR?	
13		Colour on PV	PR Vmax	
14		Doppler CW TV	TR Velocity	
15		Doppler PW	RVOT VTI	
16		Doppler CW PV	Vmax	
17		MV: Cine (plain)	MVA planimetry	
18		Colour on MV	MR?	
19		LV Papillary musc: Cine (plain)		
20		LV Apex: Cine (plain)		
21	A4C	Cine (plain)	LA area, LA Vol, RA area, RVEDD1/2/3 RV tissue Doppler, LAV (biplane), LVEF (Simpson's / estimated), RV EDS/ESA	
22		Colour on MV	MR. Regurgitant Volume.	
23		Doppler PW MV inflow	E wave, A wave, (E/A ratio), E deceleration time	
24		Doppler CW MV	Mean PG. MV VTI. MR Vmax	
25		TDI medial mitral annulus	E'	
26		TDI lateral mitral annulus	E'	
27		Zoom: Simpson's	LVEDV, LVESV, LVEF (Simpson's / estimated?)	
28		Colour on TV	TR	
29		Doppler CW TV	TR Velocity	
30		MMode	TAPSE	
31	A5C	Cine (plain)		
32		Colour on AV	AR?	
33		Doppler PW	LVOT Vmax. VTI. CO. SV. IVRT	
34		Doppler CW AV	Vmax, PeakGrad, MeanGrad. AR Vmin. PHT	
35	A2C	Cine (plain)		
36		Colour on MV	MR?	
37		Zoom:	LVEDV, LVESV, LVEF (Simpson's / estimated?) LAV (biplane)	
38	A3C	Cine (plain)		
39		Colour on MV	MR?	
40		Colour on AV	AR?	
43	Subcostal	Cine (plain)		
45		M-Mode IVC with respiration	IVC diameter, Collapse (No / <50% / >50%)	
46	3D	Cine	LV/LA/RV/RA Volumes, EF	
46	Misc / Offline	Pericardium	Pericardial effusion?	
47		Strain	GLS	

KEY

Highlighted: ESSENTIAL / IMPORTANT

PLAX/PSAX: Parasternal Long/Short Axis
A4/5/2/3C: Apical 4/5/2/3 Chamber
CW/PW: Continuous/Pulsed Wave
AV/MV/TV/PV: Aortic/Mitral/Tricuspid/Pulmonary Valve
LA/RA/LV/RV: Left/Right Atrium/Ventricle

Ao: Aorta
IAS: Inter-atrial septum
IVC: Inferior Vena Cava

Spirometry Standard Operating Procedure – CONGEST-HF

Rationale: Respiratory function assessment

Estimated duration: 5-10 minutes

Patient preparation & position:

- Sitting upright, feet on floor, arms and legs uncrossed- Tidal Volume, Respiratory Rate

Avoid:

- Smoking within 1 hour
- Alcohol consumption within 4 hours
- Vigorous exercise within 1 hour
- Tight fitting clothing

Presence of the following noted:

1. Medications and when last taken
2. Age, gender, height, weight, ethnicity

Equipment: Vitalograph spirometer, study PC, bacterial viral filters, syringe for calibration, nose clips

Technique:

- Tidal (normal) breaths are taken first
    - Nose clip in place
    - Normal breathing taken with or without mouthpiece in place. Tight seal required when mouthpiece in place
    - Breathing at normal depth
- 3 readings of adequate quality performed, or until patient unable to continue if <3 attempts possible
- Minimum 30 seconds between readings

Data

- Values recorded- TV per L (VT on Spirotrac software)
- Values recorded on study PC using study unique identifier
- Worksheet completed– source document, kept securely in study file
- Values uploaded to study eCRF